



Clinical trial results:

Capecitabine and bevacizumab ± vinorelbine as 1st line treatment in HER2/neu-negative metastatic or locally advanced inoperable breast cancer patients

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2008-003779-37 |
| Trial protocol | DE |
| Global end of trial date | 15 January 2016 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 04 August 2021 |
| First version publication date | 04 August 2021 |
| Summary attachment (see zip file) | CARIN Study Results (CARIN_CSR_E3_Synopsis_v2.0_17Okt2016.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | IOM-080-2 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00868634 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | iOMEDICO AG |
| Sponsor organisation address | Ellen-Gottlieb-Str. 19, Freiburg, Germany, 79106 |
| Public contact | Clinical Trials Information, iOMEDICO AG, 0049 761152420, info@iomedico.com |
| Scientific contact | Clinical Trials Information, iOMEDICO AG, 0049 761152420, info@iomedico.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 February 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 October 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To verify the superiority of the combination capecitabine, bevacizumab and vinorelbin compared to the combination of capecitabine and bevacizumab.

Primary endpoint: Progression free survival

Protection of trial subjects:

Independent ethics committees at all participating sites approved the protocol and all modifications. All patients provided written informed consent.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 04 February 2009 |
| 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 | Germany: 592 |
| Worldwide total number of subjects | 592 |
| EEA total number of subjects | 592 |

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) | 355 |
| From 65 to 84 years | 237 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment 1:1

Pre-assignment

Screening details:

After a patient had signed informed consent form, screening procedures for study enrollment were completed.

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 | Arm A - CAP/BEV |
|------------------|-----------------|

Arm description:

Capecitabine + bevacizumab

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

Dosage and administration details:

1000 mg/m² (twice daily, days 1-14, q3w)

| | |
|--|--------------------------|
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

15 mg/kg (day 1, q3w)

| | |
|------------------|---------------------|
| Arm title | Arm B - CAP/BEV/VIN |
|------------------|---------------------|

Arm description:

Capecitabine + bevacizumab + vinorelbine

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

Dosage and administration details:

1000 mg/m² (twice daily, days 1-14, q3w)

| | |
|--|-----------------------|
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |

| | |
|--|-----------------------|
| Routes of administration | Intravenous use |
| Dosage and administration details: 15 mg/kg (day 1, q3w) | |
| Investigational medicinal product name | Vinorelbine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 25 mg/m2 (days 1+8, q3w) | |

| Number of subjects in period 1 | Arm A - CAP/BEV | Arm B - CAP/BEV/VIN |
|---------------------------------------|-----------------|---------------------|
| Started | 297 | 295 |
| Completed | 297 | 295 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Arm A - CAP/BEV |
|-----------------------|-----------------|

Reporting group description:

Capecitabine + bevacizumab

| | |
|-----------------------|---------------------|
| Reporting group title | Arm B - CAP/BEV/VIN |
|-----------------------|---------------------|

Reporting group description:

Capecitabine + bevacizumab + vinorelbine

| Reporting group values | Arm A - CAP/BEV | Arm B - CAP/BEV/VIN | Total |
|--|-----------------|---------------------|-------|
| Number of subjects | 297 | 295 | 592 |
| 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) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| < 65 years | 192 | 163 | 355 |
| >= 65 years | 105 | 132 | 237 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 297 | 295 | 592 |

End points

End points reporting groups

| | |
|--|---------------------|
| Reporting group title | Arm A - CAP/BEV |
| Reporting group description: | |
| Capecitabine + bevacizumab | |
| Reporting group title | Arm B - CAP/BEV/VIN |
| Reporting group description: | |
| Capecitabine + bevacizumab + vinorelbine | |

Primary: PFS - Progression Free Survival

| | |
|---|---------------------------------|
| End point title | PFS - Progression Free Survival |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Time from first randomization until first signs of tumor progression or death from any cause. | |

| End point values | Arm A - CAP/BEV | Arm B - CAP/BEV/VIN | | |
|---------------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 297 | 295 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 8.8 (8.15 to 9.79) | 9.6 (8.8 to 11.2) | | |

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | Kaplan Meier Estimates |
| Comparison groups | Arm A - CAP/BEV v Arm B - CAP/BEV/VIN |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.01 |
| Variability estimate | Standard deviation |

Secondary: ORR - Overall Response Rate

| | |
|-----------------|-----------------------------|
| End point title | ORR - Overall Response Rate |
|-----------------|-----------------------------|

End point description:

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

End point timeframe:

Patients were considered evaluable for response if they had measurable disease at baseline

| End point values | Arm A - CAP/BEV | Arm B - CAP/BEV/VIN | | |
|-----------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 179 ^[1] | 162 ^[2] | | |
| Units: Number of patients | 65 | 77 | | |

Notes:

[1] - Only patients with measurable disease at baseline were evaluable

[2] - Only patients with measurable disease at baseline were evaluable

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | ORR Analysis |
| Comparison groups | Arm A - CAP/BEV v Arm B - CAP/BEV/VIN |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | ≤ 0.05 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3986 |
| upper limit | 0.9936 |
| Variability estimate | Standard deviation |

Secondary: OS - Overall Survival

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

End point description:

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

End point timeframe:

Time from randomization until death

| End point values | Arm A - CAP/BEV | Arm B - CAP/BEV/VIN | | |
|---------------------------------------|--------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 297 | 295 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 25.1 (23.06 to 28.98) | 27.2 (23.46 to 29.67) | | |

Statistical analyses

| Statistical analysis title | Kaplan Meier Estimates |
|---|---------------------------------------|
| Comparison groups | Arm A - CAP/BEV v Arm B - CAP/BEV/VIN |
| Number of subjects included in analysis | 592 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | ≤ 0.05 |
| Method | Logrank |
| Parameter estimate | Average Hazard Ratio |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.03 |
| Variability estimate | Standard deviation |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE assessment started with randomization until end of treatment plus 30 days safety follow-up
(=treatment emergent period)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Arm A - CAP/BEV |
|-----------------------|-----------------|

Reporting group description: -

| | |
|-----------------------|---------------------|
| Reporting group title | Arm B - CAP/BEV/VIN |
|-----------------------|---------------------|

Reporting group description: -

| Serious adverse events | Arm A - CAP/BEV | Arm B - CAP/BEV/VIN | |
|---|--------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 112 / 297 (37.71%) | 150 / 295 (50.85%) | |
| number of deaths (all causes) | 219 | 205 | |
| number of deaths resulting from adverse events | 18 | 25 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to bone | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Metastases to bone marrow | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metastases to central nervous system | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to liver | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| 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 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to peritoneum | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Neoplasm progression | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Tumour pain | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 3 / 295 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 3 / 297 (1.01%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phleboscclerosis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superior vena cava syndrome | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 4 / 295 (1.36%) | |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 3 / 295 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Catheter management | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chemotherapy | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiofrequency ablation of oesophagus | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 4 / 295 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disease progression | | | |
| subjects affected / exposed | 6 / 297 (2.02%) | 4 / 295 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 4 | 1 / 3 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 4 / 295 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 6 / 297 (2.02%) | 14 / 295 (4.75%) | |
| occurrences causally related to treatment / all | 2 / 6 | 7 / 15 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 4 | |
| Impaired healing | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| multi-organ failure | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pain | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 3 / 295 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ulcer | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 297 (2.02%) | 5 / 295 (1.69%) | |
| occurrences causally related to treatment / all | 1 / 6 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 3 / 295 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary artery thrombosis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 297 (1.35%) | 16 / 295 (5.42%) | |
| occurrences causally related to treatment / all | 3 / 4 | 11 / 16 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 4 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood creatine increased | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood pressure orthostatic abnormal | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Granulocyte count decreased | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Protein total decreased | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| 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 | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Fall | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury corneal | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pubis fracture | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skull fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradyarrhythmia | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure acute | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cauda equina syndrome | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic coma | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intercostal neuralgia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Leukoencephalopathy | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic intolerance | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 2 / 297 (0.67%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 3 / 295 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Diplegia | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 5 / 295 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematotoxicity | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 20 / 295 (6.78%) | |
| occurrences causally related to treatment / all | 1 / 1 | 26 / 26 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Lymphadenopathy | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 19 / 295 (6.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 22 / 22 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 4 / 297 (1.35%) | 3 / 295 (1.02%) | |
| occurrences causally related to treatment / all | 3 / 4 | 3 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Splenic infarction | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| 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 | 2 / 297 (0.67%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fissure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal ulcer | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 4 / 295 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 4 / 295 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 297 (2.36%) | 5 / 295 (1.69%) | |
| occurrences causally related to treatment / all | 4 / 7 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Mesenteric vein thrombosis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 5 / 295 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 297 (1.01%) | 6 / 295 (2.03%) | |
| occurrences causally related to treatment / all | 2 / 3 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 3 / 297 (1.01%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic pain | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eczema | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity vasculitis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive uropathy | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 3 / 295 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal disorder | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 3 / 295 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Ureteric stenosis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint effusion | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteolysis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Actinomycosis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Amoebic dysentery | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bronchitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 297 (0.67%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis rotavirus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected seroma | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 297 (1.68%) | 7 / 295 (2.37%) | |
| occurrences causally related to treatment / all | 2 / 5 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomembranous colitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 4 / 295 (1.36%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 297 (1.01%) | 4 / 295 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 4 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 2 / 295 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 297 (1.35%) | 3 / 295 (1.02%) | |
| occurrences causally related to treatment / all | 2 / 4 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 297 (0.34%) | 0 / 295 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ketoacidosis | | | |
| subjects affected / exposed | 0 / 297 (0.00%) | 1 / 295 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Arm A - CAP/BEV | Arm B - CAP/BEV/VIN | |
|---|--------------------|---------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 292 / 297 (98.32%) | 291 / 295 (98.64%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 85 / 297 (28.62%) | 66 / 295 (22.37%) | |
| occurrences (all) | 112 | 83 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 89 / 297 (29.97%) | 125 / 295 (42.37%) | |
| occurrences (all) | 102 | 155 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 17 / 297 (5.72%) | 19 / 295 (6.44%) | |
| occurrences (all) | 17 | 22 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 57 / 297 (19.19%) | 67 / 295 (22.71%) | |
| occurrences (all) | 73 | 88 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 16 / 297 (5.39%) | 15 / 295 (5.08%) | |
| occurrences (all) | 17 | 16 | |
| Pain | | | |
| subjects affected / exposed | 24 / 297 (8.08%) | 32 / 295 (10.85%) | |
| occurrences (all) | 26 | 36 | |
| Pyrexia | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 13 / 297 (4.38%) 14 | 28 / 295 (9.49%) 38 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 30 / 297 (10.10%) | 27 / 295 (9.15%) | |
| occurrences (all) | 32 | 28 | |
| Dysphonia | | | |
| subjects affected / exposed | 11 / 297 (3.70%) | 18 / 295 (6.10%) | |
| occurrences (all) | 12 | 20 | |
| Dyspnoea | | | |
| subjects affected / exposed | 34 / 297 (11.45%) | 43 / 295 (14.58%) | |
| occurrences (all) | 35 | 49 | |
| Epistaxis | | | |
| subjects affected / exposed | 34 / 297 (11.45%) | 59 / 295 (20.00%) | |
| occurrences (all) | 39 | 68 | |
| Psychiatric disorders | | | |
| Sleep disorder | | | |
| subjects affected / exposed | 19 / 297 (6.40%) | 23 / 295 (7.80%) | |
| occurrences (all) | 20 | 23 | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 23 / 297 (7.74%) | 36 / 295 (12.20%) | |
| occurrences (all) | 23 | 37 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 21 / 297 (7.07%) | 27 / 295 (9.15%) | |
| occurrences (all) | 25 | 35 | |
| Dysgeusia | | | |
| subjects affected / exposed | 28 / 297 (9.43%) | 26 / 295 (8.81%) | |
| occurrences (all) | 28 | 28 | |
| Headache | | | |
| subjects affected / exposed | 41 / 297 (13.80%) | 49 / 295 (16.61%) | |
| occurrences (all) | 48 | 63 | |
| Paraesthesia | | | |
| subjects affected / exposed | 18 / 297 (6.06%) | 17 / 295 (5.76%) | |
| occurrences (all) | 22 | 21 | |

| | | | |
|--|--------------------------|---------------------------|--|
| Polyneuropathy subjects affected / exposed occurrences (all) | 22 / 297 (7.41%) 24 | 45 / 295 (15.25%) 48 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 12 / 297 (4.04%) 16 | 45 / 295 (15.25%) 58 | |
| Leukopenia subjects affected / exposed occurrences (all) | 8 / 297 (2.69%) 9 | 83 / 295 (28.14%) 171 | |
| Neutropenia subjects affected / exposed occurrences (all) | 10 / 297 (3.37%) 13 | 80 / 295 (27.12%) 155 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 7 / 297 (2.36%) 7 | 15 / 295 (5.08%) 16 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 26 / 297 (8.75%) 31 | 43 / 295 (14.58%) 53 | |
| Constipation subjects affected / exposed occurrences (all) | 43 / 297 (14.48%) 52 | 67 / 295 (22.71%) 82 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 92 / 297 (30.98%) 140 | 83 / 295 (28.14%) 117 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 16 / 297 (5.39%) 17 | 26 / 295 (8.81%) 27 | |
| Nausea subjects affected / exposed occurrences (all) | 96 / 297 (32.32%) 119 | 129 / 295 (43.73%) 179 | |
| Stomatitis subjects affected / exposed occurrences (all) | 22 / 297 (7.41%) 24 | 25 / 295 (8.47%) 35 | |
| Vomiting | | | |

| | | | |
|---|--------------------|--------------------|--|
| subjects affected / exposed | 39 / 297 (13.13%) | 51 / 295 (17.29%) | |
| occurrences (all) | 50 | 64 | |
| Abdominal pain | | | |
| subjects affected / exposed | 16 / 297 (5.39%) | 14 / 295 (4.75%) | |
| occurrences (all) | 20 | 18 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 20 / 297 (6.73%) | 59 / 295 (20.00%) | |
| occurrences (all) | 22 | 61 | |
| Erythema | | | |
| subjects affected / exposed | 18 / 297 (6.06%) | 8 / 295 (2.71%) | |
| occurrences (all) | 18 | 9 | |
| Nail disorder | | | |
| subjects affected / exposed | 17 / 297 (5.72%) | 11 / 295 (3.73%) | |
| occurrences (all) | 17 | 12 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 195 / 297 (65.66%) | 119 / 295 (40.34%) | |
| occurrences (all) | 305 | 174 | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 23 / 297 (7.74%) | 19 / 295 (6.44%) | |
| occurrences (all) | 38 | 28 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 22 / 297 (7.41%) | 29 / 295 (9.83%) | |
| occurrences (all) | 24 | 30 | |
| Back pain | | | |
| subjects affected / exposed | 20 / 297 (6.73%) | 28 / 295 (9.49%) | |
| occurrences (all) | 21 | 29 | |
| Bone pain | | | |
| subjects affected / exposed | 26 / 297 (8.75%) | 24 / 295 (8.14%) | |
| occurrences (all) | 28 | 27 | |
| Muscle spasms | | | |
| subjects affected / exposed | 7 / 297 (2.36%) | 16 / 295 (5.42%) | |
| occurrences (all) | 7 | 19 | |
| Pain in extremity | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 20 / 297 (6.73%) 22 | 26 / 295 (8.81%) 29 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 27 / 297 (9.09%) | 32 / 295 (10.85%) | |
| occurrences (all) | 32 | 47 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 28 / 297 (9.43%) | 29 / 295 (9.83%) | |
| occurrences (all) | 35 | 33 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 39 / 297 (13.13%) | 45 / 295 (15.25%) | |
| occurrences (all) | 41 | 57 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 09 June 2009 | A first revision of the initial study protocol introduced the project "Translational research" |
| 23 September 2009 | The substantial amendment 1 introduced the project "Epigenetic Profiling of Plasma DNA in Response to Chemotherapy Treatment" |
| 14 March 2011 | The substantial amendment 2 included the capture of laboratory values extended even to laboratory values considered non-pathological, and the capture of tumor evaluations independent of individual treatment cycles. |
| 09 August 2011 | The substantial amendment 3 included the increase of the patient number from initial 400 to 600, and the changeover of capecitabine and bevacizumab to articles of trade. |
| 21 October 2014 | The substantial amendment 4 issued the classification of the trial. The trial phase was changed from IIb to phase III. Further, the number of events for the primary endpoint analysis was reduced due to the unexpected high drop-out rate. The original sample size calculation assumed 494 events, the amended sample size included at least 441 events, yielding 75% power to detect a PFS difference between treatment arms. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported