



Clinical trial results:

A prospective randomised Phase III trial to evaluate optimal treatment duration of first-line bevacizumab in combination with carboplatin and paclitaxel in patients with primary epithelial ovarian, fallopian tube or peritoneal cancer.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2011-001015-32 |
| Trial protocol | DE FR FI NO DK SE |
| Global end of trial date | 26 November 2020 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 21 July 2022 |
| First version publication date | 21 July 2022 |
| Summary attachment (see zip file) | OVAR17_E3-Synopse_V01F_2021-11- (OVAR17_E3-Synopse_V01F_2021-11-09_signed.pdf) |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | AGO-OVAR17 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|---------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01462890 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | GINECO OV118: ENGOT Ov-15 Trial |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AGO Research GmbH |
| Sponsor organisation address | Kaiser-Friedrich-Ring 71, Wiesbaden, Germany, 65185 |
| Public contact | Study Office, AGO Research GmbH, 0049 6118804 670, gelser@ago-ovar.de |
| Scientific contact | Study Office, AGO Research GmbH, 0049 6118804 670, gelser@ago-ovar.de |

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 | 07 January 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 November 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare progression-free survival (PFS) (by RECIST v1.1, clinical or symptomatic) of patients randomized to front-line paclitaxel/carboplatin with bevacizumab for 15 months or 30 months.

Protection of trial subjects:

The study consisted of a screening/baseline period, a treatment period and a posttreatment or follow-up period.

Background therapy:

--

Evidence for comparator:

--

| | |
|---|--------------|
| Actual start date of recruitment | 01 July 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Norway: 12 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | Denmark: 8 |
| Country: Number of subjects enrolled | Finland: 14 |
| Country: Number of subjects enrolled | France: 126 |
| Country: Number of subjects enrolled | Germany: 764 |
| Worldwide total number of subjects | 927 |
| EEA total number of subjects | 927 |

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) | 575 |
| From 65 to 84 years | 350 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of a screening/baseline period, a treatment period and a posttreatment or follow-up period.

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 | Standard arm |

Arm description:

Bevacizumab, Paclitaxel, Carboplatin

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

15 mg/kg on day 1 every 3 weeks (together with chemotherapy treatment) up to and including cycle 21 or 22

| | |
|------------------|------------------|
| Arm title | Experimental arm |
|------------------|------------------|

Arm description:

Bevacizumab, Paclitaxel, Carboplatin

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

Dosage and administration details:

15 mg/kg on day 1 every 3 weeks (together with chemotherapy treatment) up to and including cycle 43 or 44

| Number of subjects in period 1 | Standard arm | Experimental arm |
|--------------------------------|--------------|------------------|
| Started | 464 | 463 |
| Completed | 448 | 442 |
| Not completed | 16 | 21 |
| Consent withdrawn by subject | 7 | 5 |

| | | |
|--|---|---|
| Disease progression | 1 | - |
| Adverse event, non-fatal | 4 | 4 |
| Death | 2 | 4 |
| Another urgent surgery | 1 | - |
| Refused treatment | - | 2 |
| Intercurrent illness | 1 | 4 |
| Further therapy outside study (sponsor decision) | - | 1 |
| Incomplete wound healing (sponsor decision) | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall trial |
| Reporting group description: - | |

| Reporting group values | Overall trial | Total | |
|------------------------------------|---------------|-------|--|
| Number of subjects | 927 | 927 | |
| Age categorical | | | |
| female patients 18 years and older | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 575 | 575 | |
| From 65-84 years | 350 | 350 | |
| 85 years and over | 2 | 2 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 927 | 927 | |
| Male | 0 | 0 | |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | Standard arm |
| Reporting group description: Bevacizumab, Paclitaxel, Carboplatin | |
| Reporting group title | Experimental arm |
| Reporting group description: Bevacizumab, Paclitaxel, Carboplatin | |

Primary: Progression-free survival (PFS)

| | |
|---|---------------------------------|
| End point title | Progression-free survival (PFS) |
| End point description: | |
| End point type | Primary |
| End point timeframe: Progression-free survival (PFS) is defined as the time from the date of randomization to investigator assessed disease progression. | |

| End point values | Standard arm | Experimental arm | | |
|-----------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 464 | 463 | | |
| Units: months | | | | |
| number (not applicable) | 24.2 | 26.0 | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | Primary statistical analysis |
| Comparison groups | Standard arm v Experimental arm |
| Number of subjects included in analysis | 927 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.15 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events occurring during the clinical trial or within 30 days after treatment discontinuation

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Standard arm |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|------------------|
| Reporting group title | Experimental arm |
|-----------------------|------------------|

Reporting group description: -

| Serious adverse events | Standard arm | Experimental arm | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 199 / 448 (44.42%) | 204 / 442 (46.15%) | |
| number of deaths (all causes) | 257 | 277 | |
| number of deaths resulting from adverse events | 8 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Metastases to kidney | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraneoplastic cerebellar degeneration | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 3 / 448 (0.67%) | 3 / 442 (0.68%) | |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 448 (2.46%) | 16 / 442 (3.62%) | |
| occurrences causally related to treatment / all | 12 / 12 | 17 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 4 / 442 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Hypertensive emergency | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphocele | | | |
| subjects affected / exposed | 7 / 448 (1.56%) | 9 / 442 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic venous thrombosis | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 4 / 442 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Bladder catheter removal | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder catheter replacement | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central venous catheterisation | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 3 / 442 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 3 / 448 (0.67%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Device leakage | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 448 (0.67%) | 5 / 442 (1.13%) | |
| occurrences causally related to treatment / all | 0 / 4 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 20 / 448 (4.46%) | 20 / 442 (4.52%) | |
| occurrences causally related to treatment / all | 3 / 26 | 7 / 32 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Hernia obstructive | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injection site reaction | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 11 / 448 (2.46%) | 16 / 442 (3.62%) | |
| occurrences causally related to treatment / all | 0 / 12 | 4 / 18 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 3 / 442 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 3 / 448 (0.67%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |

| | | | |
|--|-----------------|------------------|--|
| Female genital tract fistula subjects affected / exposed | 3 / 448 (0.67%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vaginal haemorrhage subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| 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 / 448 (1.34%) | 11 / 442 (2.49%) | |
| occurrences causally related to treatment / all | 2 / 6 | 4 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion subjects affected / exposed | 4 / 448 (0.89%) | 6 / 442 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary arterial hypertension subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (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 | 6 / 448 (1.34%) | 7 / 442 (1.58%) | |
| occurrences causally related to treatment / all | 3 / 6 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Respiratory disorder | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystoscopy | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder injury | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal injury | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (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 | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Incisional hernia | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seroma | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (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 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulna fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urostomy complication | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiovascular disorder | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 3 / 442 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| 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 | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 448 (1.12%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 3 / 5 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intercostal neuralgia | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial venous sinus thrombosis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Monoparesis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nerve compression | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (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 | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 448 (0.00%) | 3 / 442 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Posterior reversible encephalopathy syndrome | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 448 (1.34%) | 5 / 442 (1.13%) | |
| occurrences causally related to treatment / all | 2 / 7 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 9 / 448 (2.01%) | 4 / 442 (0.90%) | |
| occurrences causally related to treatment / all | 2 / 9 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 4 / 448 (0.89%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Lens dislocation | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 3 / 442 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 17 / 448 (3.79%) | 16 / 442 (3.62%) | |
| occurrences causally related to treatment / all | 3 / 21 | 3 / 20 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 6 / 442 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal wall haematoma | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute abdomen | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fistula | | | |
| subjects affected / exposed | 4 / 448 (0.89%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 10 / 448 (2.23%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 17 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bowel movement irregularity | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic fistula | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 448 (0.00%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 6 / 448 (1.34%) | 8 / 442 (1.81%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diaphragmatic hernia | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 448 (2.01%) | 6 / 442 (1.36%) | |
| occurrences causally related to treatment / all | 3 / 9 | 2 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea haemorrhagic | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal stenosis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer perforation | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocutaneous fistula | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecal incontinence | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal motility disorder | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 448 (0.00%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileal fistula | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 9 / 448 (2.01%) | 11 / 442 (2.49%) | |
| occurrences causally related to treatment / all | 3 / 9 | 0 / 11 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal fistula | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 448 (0.22%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesenteric artery embolism | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 5 / 442 (1.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral cavity fistula | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sigmoiditis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal perforation | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 15 / 448 (3.35%) | 7 / 442 (1.58%) | |
| occurrences causally related to treatment / all | 2 / 15 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 8 / 442 (1.81%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (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 | | | |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Bladder disorder | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 7 / 448 (1.56%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proteinuria | | | |
| subjects affected / exposed | 3 / 448 (0.67%) | 6 / 442 (1.36%) | |
| occurrences causally related to treatment / all | 3 / 3 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelocaliectasis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (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 | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract disorder | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Basedow's disease | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (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 | | | |

| | | | |
|---|-----------------|-----------------|--|
| Arthralgia | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 3 / 442 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fistula | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatic disorder | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 448 (0.00%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal wall infection | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess of salivary gland | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridial infection | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 3 / 448 (0.67%) | 3 / 442 (0.68%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 5 / 448 (1.12%) | 4 / 442 (0.90%) | |
| occurrences causally related to treatment / all | 1 / 5 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterobacter infection | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterococcal infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin abscess | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Helicobacter gastritis | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected cyst | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected lymphocele | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 448 (1.12%) | 6 / 442 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 5 / 442 (1.13%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle abscess | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis media | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic abscess | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 4 / 442 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psoas abscess | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethritis | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 7 / 448 (1.56%) | 6 / 442 (1.36%) | |
| occurrences causally related to treatment / all | 2 / 7 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vaginal abscess | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| 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 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suture rupture | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Wound haemorrhage | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 448 (0.45%) | 5 / 442 (1.13%) | |
| occurrences causally related to treatment / all | 0 / 2 | 3 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hypercalcaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 448 (0.22%) | 0 / 442 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 448 (0.00%) | 1 / 442 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 448 (0.67%) | 2 / 442 (0.45%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Standard arm | Experimental arm | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 445 / 448 (99.33%) | 439 / 442 (99.32%) | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 33 / 448 (7.37%) | 35 / 442 (7.92%) | |
| occurrences (all) | 61 | 62 | |
| Hypertension | | | |
| subjects affected / exposed | 168 / 448 (37.50%) | 232 / 442 (52.49%) | |
| occurrences (all) | 546 | 783 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 40 / 448 (8.93%) | 53 / 442 (11.99%) | |
| occurrences (all) | 91 | 101 | |
| Fatigue | | | |
| subjects affected / exposed | 204 / 448 (45.54%) | 208 / 442 (47.06%) | |
| occurrences (all) | 421 | 447 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 23 / 448 (5.13%) | 24 / 442 (5.43%) | |
| occurrences (all) | 34 | 36 | |
| Mucosal inflammation | | | |

| | | | |
|---|-------------------|--------------------|--|
| subjects affected / exposed | 67 / 448 (14.96%) | 65 / 442 (14.71%) | |
| occurrences (all) | 114 | 111 | |
| Oedema | | | |
| subjects affected / exposed | 20 / 448 (4.46%) | 35 / 442 (7.92%) | |
| occurrences (all) | 28 | 53 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 26 / 448 (5.80%) | 35 / 442 (7.92%) | |
| occurrences (all) | 30 | 47 | |
| Pain | | | |
| subjects affected / exposed | 45 / 448 (10.04%) | 28 / 442 (6.33%) | |
| occurrences (all) | 71 | 59 | |
| Pyrexia | | | |
| subjects affected / exposed | 47 / 448 (10.49%) | 53 / 442 (11.99%) | |
| occurrences (all) | 69 | 66 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 15 / 448 (3.35%) | 32 / 442 (7.24%) | |
| occurrences (all) | 22 | 55 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 29 / 448 (6.47%) | 25 / 442 (5.66%) | |
| occurrences (all) | 33 | 31 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 23 / 448 (5.13%) | 40 / 442 (9.05%) | |
| occurrences (all) | 28 | 47 | |
| Dysphonia | | | |
| subjects affected / exposed | 19 / 448 (4.24%) | 35 / 442 (7.92%) | |
| occurrences (all) | 25 | 41 | |
| Dyspnoea | | | |
| subjects affected / exposed | 82 / 448 (18.30%) | 88 / 442 (19.91%) | |
| occurrences (all) | 119 | 133 | |
| Epistaxis | | | |
| subjects affected / exposed | 86 / 448 (19.20%) | 101 / 442 (22.85%) | |
| occurrences (all) | 106 | 150 | |
| Psychiatric disorders | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| Depression subjects affected / exposed occurrences (all) | 23 / 448 (5.13%) 27 | 23 / 442 (5.20%) 31 | |
| Insomnia subjects affected / exposed occurrences (all) | 47 / 448 (10.49%) 71 | 41 / 442 (9.28%) 60 | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 18 / 448 (4.02%) 32 | 27 / 442 (6.11%) 54 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 30 / 448 (6.70%) 43 | 26 / 442 (5.88%) 40 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 23 / 448 (5.13%) 29 | 34 / 442 (7.69%) 40 | |
| Headache subjects affected / exposed occurrences (all) | 70 / 448 (15.63%) 124 | 95 / 442 (21.49%) 160 | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 49 / 448 (10.94%) 90 | 47 / 442 (10.63%) 90 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 40 / 448 (8.93%) 48 | 47 / 442 (10.63%) 71 | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 144 / 448 (32.14%) 263 | 129 / 442 (29.19%) 284 | |
| Polyneuropathy subjects affected / exposed occurrences (all) | 81 / 448 (18.08%) 141 | 98 / 442 (22.17%) 182 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 83 / 448 (18.53%) 202 | 87 / 442 (19.68%) 196 | |
| Leukopenia | | | |

| | | | |
|--|--------------------|--------------------|--|
| subjects affected / exposed | 37 / 448 (8.26%) | 49 / 442 (11.09%) | |
| occurrences (all) | 111 | 138 | |
| Neutropenia | | | |
| subjects affected / exposed | 63 / 448 (14.06%) | 80 / 442 (18.10%) | |
| occurrences (all) | 165 | 219 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 36 / 448 (8.04%) | 39 / 442 (8.82%) | |
| occurrences (all) | 79 | 90 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 21 / 448 (4.69%) | 27 / 442 (6.11%) | |
| occurrences (all) | 25 | 36 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 92 / 448 (20.54%) | 96 / 442 (21.72%) | |
| occurrences (all) | 132 | 152 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 47 / 448 (10.49%) | 60 / 442 (13.57%) | |
| occurrences (all) | 80 | 82 | |
| Constipation | | | |
| subjects affected / exposed | 170 / 448 (37.95%) | 169 / 442 (38.24%) | |
| occurrences (all) | 282 | 322 | |
| Diarrhoea | | | |
| subjects affected / exposed | 141 / 448 (31.47%) | 117 / 442 (26.47%) | |
| occurrences (all) | 291 | 256 | |
| Nausea | | | |
| subjects affected / exposed | 202 / 448 (45.09%) | 180 / 442 (40.72%) | |
| occurrences (all) | 386 | 348 | |
| Stomatitis | | | |
| subjects affected / exposed | 62 / 448 (13.84%) | 72 / 442 (16.29%) | |
| occurrences (all) | 93 | 106 | |
| Vomiting | | | |
| subjects affected / exposed | 111 / 448 (24.78%) | 88 / 442 (19.91%) | |
| occurrences (all) | 171 | 135 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|--------------------------|--------------------|--|
| Alopecia subjects affected / exposed | 288 / 448 (64.29%) | 294 / 442 (66.52%) | |
| | occurrences (all) 354 | 364 | |
| Rash subjects affected / exposed | 20 / 448 (4.46%) | 31 / 442 (7.01%) | |
| | occurrences (all) 20 | 39 | |
| Renal and urinary disorders | | | |
| Proteinuria subjects affected / exposed | 42 / 448 (9.38%) | 73 / 442 (16.52%) | |
| occurrences (all) | 95 | 262 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed | 127 / 448 (28.35%) | 138 / 442 (31.22%) | |
| occurrences (all) | 225 | 295 | |
| Back pain subjects affected / exposed | 35 / 448 (7.81%) | 53 / 442 (11.99%) | |
| occurrences (all) | 38 | 69 | |
| Bone pain subjects affected / exposed | 47 / 448 (10.49%) | 46 / 442 (10.41%) | |
| occurrences (all) | 75 | 68 | |
| Musculoskeletal pain subjects affected / exposed | 22 / 448 (4.91%) | 36 / 442 (8.14%) | |
| occurrences (all) | 39 | 54 | |
| Myalgia subjects affected / exposed | 84 / 448 (18.75%) | 91 / 442 (20.59%) | |
| occurrences (all) | 149 | 171 | |
| Pain in extremity subjects affected / exposed | 59 / 448 (13.17%) | 59 / 442 (13.35%) | |
| occurrences (all) | 97 | 85 | |
| Infections and infestations | | | |
| Cystitis subjects affected / exposed | 54 / 448 (12.05%) | 49 / 442 (11.09%) | |
| occurrences (all) | 88 | 92 | |
| Nasopharyngitis subjects affected / exposed | 47 / 448 (10.49%) | 63 / 442 (14.25%) | |
| occurrences (all) | 59 | 82 | |

| | | | |
|--|--------------------------|--------------------------|--|
| Urinary tract infection subjects affected / exposed occurrences (all) | 66 / 448 (14.73%) 102 | 85 / 442 (19.23%) 133 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 30 / 448 (6.70%) 58 | 39 / 442 (8.82%) 65 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 19 December 2011 | New Protocol V03 F (21/11/2011): Specification of exclusion criteria no. 22, Additions regarding the second opinion pathology for patients from France, Update of Patient Information and Informed Consent Form |
| 27 March 2013 | New Protokoll V05 F (14/03/2013): Update of the statistical considerations including increase of the number of patients to 900, Update of Patient Information and Informed Consent Form |
| 19 July 2013 | Update of Patient Information and Informed Consent Form due to "Roter-Hand-Brief" of 15.05.2013 |
| 06 January 2015 | Additional Patient Information and Informed Consent Form due to changes in the German Summary of Product Characteristics Avastin 09/2014 |
| 28 December 2016 | New Protocol V06 F (15/11/2016): Wording for the efficacy follow-up period has been corrected or rather adjusted |
| 24 September 2020 | Amendment No. 1 (31/08/2020) to Protocol V06 F: Removes PFS events as a condition of the timing of the data cutoff for primary analysis |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported