

**Clinical trial results:
A Multi-Centre Randomised Clinical Trial of Biomarker-Driven
Maintenance Treatment for First-Line Metastatic Colorectal Cancer
(MODUL)****Summary**

| | |
|--------------------------|---|
| EudraCT number | 2014-001017-61 |
| Trial protocol | IT GB DE PT DK SK NL FR SE BE GR ES SI CY |
| Global end of trial date | 24 March 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v3 (current) |
| This version publication date | 05 April 2024 |
| First version publication date | 12 June 2020 |
| Version creation reason | |

Trial information**Trial identification**

| | |
|-----------------------|---------|
| Sponsor protocol code | MO29112 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02291289 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 24 March 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 May 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 March 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate progression free survival (PFS).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 17 April 2015 |
| 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 | Argentina: 8 |
| Country: Number of subjects enrolled | Belgium: 44 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 13 |
| Country: Number of subjects enrolled | Brazil: 61 |
| Country: Number of subjects enrolled | Denmark: 18 |
| Country: Number of subjects enrolled | Egypt: 10 |
| Country: Number of subjects enrolled | France: 75 |
| Country: Number of subjects enrolled | Germany: 184 |
| Country: Number of subjects enrolled | Greece: 47 |
| Country: Number of subjects enrolled | Italy: 163 |
| Country: Number of subjects enrolled | Mexico: 31 |
| Country: Number of subjects enrolled | Netherlands: 32 |
| Country: Number of subjects enrolled | Poland: 24 |
| Country: Number of subjects enrolled | Portugal: 17 |
| Country: Number of subjects enrolled | Korea, Republic of: 31 |
| Country: Number of subjects enrolled | Russian Federation: 20 |
| Country: Number of subjects enrolled | Serbia: 10 |
| Country: Number of subjects enrolled | Slovakia: 2 |
| Country: Number of subjects enrolled | Spain: 113 |
| Country: Number of subjects enrolled | Sweden: 8 |
| Country: Number of subjects enrolled | Türkiye: 40 |
| Country: Number of subjects enrolled | United Kingdom: 90 |

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Slovenia: 3 |
| Worldwide total number of subjects | 1044 |
| EEA total number of subjects | 730 |

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) | 614 |
| From 65 to 84 years | 424 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

To be eligible for the study, subjects provided a primary tumour sample for biomarker assessment. This sample came from the original diagnosis and was used for the biomarker assessment which determined treatment assignment during the Maintenance Treatment Phase.

Period 1

| | |
|------------------------------|---------------------------|
| Period 1 title | Induction Treatment Phase |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1: Induction Phase (IP) |

Arm description:

Included participants with v-raf murine sarcoma viral oncogene homolog B1 mutation positive (BRAFmut)/human epidermal growth factor receptor 2 negative (HER2-)/microsatellite stable (MSS)/rat sarcoma wild type (RASwt). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment.

| | |
|--|--|
| Arm type | Induction Treatment |
| Investigational medicinal product name | 5-fluorouracil (5-FU), leucovorin calcium (LV), and Oxaliplatin (FOLFOX) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered per the Investigator's discretion in accordance with locally approved prescribing information.

| | |
|--|-----------------------|
| Investigational medicinal product name | 5-FU/LV |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1600-2400 mg/m² 5-FU via 46-hour IV infusion in combination with 400 mg/m² LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression or death from any cause, whichever occurs first.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

| | |
|------------------|---------------|
| Arm title | Cohort 2 (IP) |
|------------------|---------------|

Arm description:

Included participants with BRAFwt. All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment.

| | |
|--|--|
| Arm type | Induction Treatment |
| Investigational medicinal product name | 5-fluorouracil (5-FU), leucovorin calcium (LV), and Oxaliplatin (FOLFOX) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered per the Investigator's discretion in accordance with locally approved prescribing information.

| | |
|--|-----------------------|
| Investigational medicinal product name | 5-FU/LV |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1600-2400 mg/m² 5-FU via 46-hour IV infusion in combination with 400 mg/m² LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression or death from any cause, whichever occurs first.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

| | |
|------------------|---------------|
| Arm title | Cohort 3 (IP) |
|------------------|---------------|

Arm description:

Included participants with human epidermal growth factor receptor 2 positive (HER2+). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment.

| | |
|--|--|
| Arm type | Induction Treatment |
| Investigational medicinal product name | 5-fluorouracil (5-FU), leucovorin calcium (LV), and Oxaliplatin (FOLFOX) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered per the Investigator's discretion in accordance with locally approved prescribing information.

| | |
|--|-----------------------|
| Investigational medicinal product name | 5-FU/LV |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1600-2400 mg/m² 5-FU via 46-hour IV infusion in combination with 400 mg/m² LV via 2-hour

infusion on Day 1 of every 2-week cycle until disease progression or death from any cause, whichever occurs first.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

| | |
|------------------|---------------|
| Arm title | Cohort 4 (IP) |
|------------------|---------------|

Arm description:

Included participants with HER2-/high microsatellite instability (MSI-H); HER2-/MSS/v-raf murine sarcoma viral oncogene homolog B1 wild type (BRAFWT); HER2-/MSS/BRAFmut/rat sarcoma mutation positive (RASmut). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment.

| | |
|--|--|
| Arm type | Induction Treatment |
| Investigational medicinal product name | 5-fluorouracil (5-FU), leucovorin calcium (LV), and Oxaliplatin (FOLFOX) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered per the Investigator's discretion in accordance with locally approved prescribing information.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

| | |
|--|-----------------------|
| Investigational medicinal product name | 5-FU/LV |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1600-2400 mg/m² 5-FU via 46-hour IV infusion in combination with 400 mg/m² LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression or death from any cause, whichever occurs first.

| Number of subjects in period 1 | Cohort 1: Induction Phase (IP) | Cohort 2 (IP) | Cohort 3 (IP) |
|---------------------------------------|--------------------------------|---------------|---------------|
| Started | 93 | 635 | 6 |
| Completed | 63 | 460 | 5 |
| Not completed | 30 | 175 | 1 |
| Consent withdrawn by subject | - | 24 | - |
| Physician decision | - | 3 | - |
| Non-Compliance | - | 1 | - |
| Adverse Event | - | 3 | - |
| Death | 25 | 111 | 1 |
| Reason Not Specified | - | 4 | - |
| Lost to follow-up | 1 | 12 | - |
| Missing | 4 | 14 | - |
| Protocol deviation | - | 3 | - |

| Number of subjects in period 1 | Cohort 4 (IP) |
|---------------------------------------|---------------|
| Started | 310 |
| Completed | 135 |
| Not completed | 175 |
| Consent withdrawn by subject | 18 |
| Physician decision | 1 |
| Non-Compliance | 1 |
| Adverse Event | 1 |
| Death | 82 |
| Reason Not Specified | 7 |
| Lost to follow-up | 9 |
| Missing | 54 |
| Protocol deviation | 2 |

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Maintenance Treatment Phase |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|--|---|
| Arm title | Cohort 1: 5-FU/LV,cetuximab,vemurafenib |
| Arm description: | |
| Participants with v-raf murine sarcoma viral oncogene homolog B1 mutation positive (BRAFMut)/human epidermal growth factor receptor 2 negative (HER2-)/microsatellite stable (MSS)/rat sarcoma wild type (RASwt) received 1600-2400 milligrams per square meter (mg/m ²) 5-FU via 46-hour intravenous (IV) infusion in combination with 400 mg/m ² LV via 2-hour infusion on Day 1 of every 2-week cycle with 500 mg/m ² cetuximab via infusion on Day 1 of every 2-week cycle and 960 milligrams (mg) vemurafenib twice daily (BID) by mouth. | |
| Arm type | Experimental |
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 500 mg/m ² via IV infusion on Day 1 of every 2-week cycle | |
| Investigational medicinal product name | 5-FU/LV |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 1600-2400 mg/m ² 5-FU via 46-hour IV infusion in combination with 400 mg/m ² LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression per the Investigator's assessment using modified Response Evaluation Criteria in Solid Tumors or death from any cause, whichever occurs first. | |
| Investigational medicinal product name | Vemurafenib |
| Investigational medicinal product code | |
| Other name | RO5185426 |
| Pharmaceutical forms | Solution for infusion, Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 960 mg vemurafenib BID by mouth | |

| | |
|---|--|
| Arm title | Cohort 1 Control: 5-FU/LV or capecitabine, bevacizumab |
| Arm description: | |
| Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | Avastin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information | |
| Investigational medicinal product name | 5-FU/LV or capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Per Investigator's discretion: 1600-2400 mg/m ² administered via 46-hour IV infusion on Day 1 of | |

every 2-week cycle and LV 400 mg/m² administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m² twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

| | |
|------------------|--|
| Arm title | Cohort 2: 5-FU/LV or capecitabine, bevacizumab, atezolizumab |
|------------------|--|

Arm description:

Participants with BRAFwt received fluoropyrimidine (1600-2400 mg/m² 5-FU via 46-hour IV infusion in combination with 400 mg/m² LV via 2-hour infusion on Day 1 of every 2-week cycle or 1000 mg/m² twice-daily capecitabine BID by mouth on Days 1-14 every 2 weeks followed by a 1-week break) with 5 milligrams per kilogram (mg/kg) bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle and 800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | 5-FU/LV or capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m² administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m² administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m² twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

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

Dosage and administration details:

800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle, or a fixed dose of 840 mg

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

| | |
|------------------|--|
| Arm title | Cohort 2 Control: 5-FU/LV or capecitabine, bevacizumab |
|------------------|--|

Arm description:

Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

| | |
|--|-------------------------|
| Investigational medicinal product name | 5-FU/LV or capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m² administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m² administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m² twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

| | |
|------------------|---|
| Arm title | Cohort 3: capecitabine, trastuzumab, pertuzumab |
|------------------|---|

Arm description:

Participants with human epidermal growth factor receptor 2 positive (HER2+) received 1000 mg/m² twice-daily capecitabine BID by mouth on Days 1-14 every 2 weeks followed by a 1-week break with trastuzumab by IV infusion on Day 1 of every 3-week treatment cycle at an initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses, and pertuzumab by IV infusion on Day 1 of each 3-week treatment cycle at an initial fixed loading dose of 840 mg followed by 420 mg for subsequent doses.

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

Dosage and administration details:

1000 mg/m² twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks

| | |
|--|-----------------------|
| Investigational medicinal product name | Pertuzumab |
| Investigational medicinal product code | |
| Other name | RO4368451 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Initial fixed loading dose of 840 mg followed by 420 mg for subsequent doses by IV infusion on Day 1 of each 3-week treatment cycle

| | |
|--|---|
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | Herceptin; RO0452317 |
| Pharmaceutical forms | Solution for infusion, Powder and solvent for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses by IV infusion on Day 1 of every 3-week treatment cycle

| | |
|------------------|---|
| Arm title | Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab |
|------------------|---|

Arm description:

Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

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

Dosage and administration details:
5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

| | |
|--|-------------------------|
| Investigational medicinal product name | 5-FU/LV or capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m² administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m² administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m² twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

| | |
|------------------|------------------------------------|
| Arm title | Cohort 4: Cobimetinib,atezolizumab |
|------------------|------------------------------------|

Arm description:

Participants with HER2-/high microsatellite instability (MSI-H); HER2-/MSS/v-raf murine sarcoma viral oncogene homolog B1 wild type (BRAFWT); HER2-/MSS/BRAFmut/rat sarcoma mutation positive (RASmut) received 60 mg cobimetinib orally for 3 weeks followed by a 1-week treatment break and atezolizumab at a fixed dose of 840 mg via 60-minute IV infusion on Day 1 of every 2-week cycle.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | RO5541267 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle, or a fixed dose of 840 mg

| | |
|--|--------------------|
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | RO5514041 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

60 mg orally once daily for 3 weeks followed by a 1-week treatment break

| | |
|------------------|---|
| Arm title | Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab |
|------------------|---|

Arm description:

Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

| | |
|--|-------------------------|
| Investigational medicinal product name | 5-FU/LV or capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m² administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m² administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m² twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

| Number of subjects in period 2 ^[1] | Cohort 1: 5-FU/LV, cetuximab, vemurafenib | Cohort 1 Control: 5-FU/LV or capecitabine, bevacizumab | Cohort 2: 5-FU/LV or capecitabine, bevacizumab, atezolizumab |
|---|---|--|--|
| | Started | 40 | 20 |
| Completed | 6 | 2 | 66 |
| Not completed | 34 | 18 | 231 |
| Physician decision | 2 | - | 3 |
| Non-Compliance | 1 | - | 2 |
| Consent withdrawn by subject | - | - | 15 |
| Study Ended by Sponsor | 1 | - | - |
| Adverse Event | - | - | 1 |
| Death | 29 | 16 | 188 |
| Not Treated | - | 2 | - |
| Reason Not Specified | - | - | 7 |
| Lost to follow-up | 1 | - | 15 |

| Number of subjects in period 2 ^[1] | Cohort 2 Control: 5-FU/LV or capecitabine, bevacizumab | Cohort 3: capecitabine, trastuzumab, pertuzumab | Cohort 3 Control: 5-FU/LV or capecitabine, bevacizumab |
|---|--|---|--|
| | Started | 148 | 3 |
| Completed | 21 | 0 | 1 |
| Not completed | 127 | 3 | 1 |
| Physician decision | - | - | - |
| Non-Compliance | 1 | - | - |
| Consent withdrawn by subject | 12 | - | - |
| Study Ended by Sponsor | - | - | - |
| Adverse Event | 1 | - | - |
| Death | 107 | 1 | 1 |
| Not Treated | - | - | - |
| Reason Not Specified | 2 | 1 | - |
| Lost to follow-up | 4 | 1 | - |

| Number of subjects in period 2 ^[1] | Cohort 4: Cobimetinib, atezolizumab | Cohort 4 Control: 5-FU/LV or capecitabine, bevacizumab |
|---|-------------------------------------|--|
| | | |

| | | |
|------------------------------|----|----|
| Started | 65 | 34 |
| Completed | 12 | 6 |
| Not completed | 53 | 28 |
| Physician decision | 1 | 3 |
| Non-Compliance | - | - |
| Consent withdrawn by subject | 2 | 3 |
| Study Ended by Sponsor | - | - |
| Adverse Event | - | - |
| Death | 46 | 19 |
| Not Treated | - | - |
| Reason Not Specified | 1 | - |
| Lost to follow-up | 3 | 3 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants initially received study treatment during the Induction Treatment Phase. Next, participants within each cohort based on biomarker status were randomized to either an experimental arm or control arm per cohort in the Maintenance Treatment Phase. BRAFmut participants experiencing early disease progression during induction treatment had the option of proceeding immediately to receive second-line treatment in the separate Early Progression Period.

Period 3

| | |
|------------------------------|---------------------------|
| Period 3 title | Early Disease Progression |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|----------------------------------|
| Arm title | Early Progressing BRAFmut Cohort |
|------------------|----------------------------------|

Arm description:

BRAFmut participants experiencing early disease progression during induction treatment had the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib if their primary tumour was MSS, or with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab if their primary tumour was MSI-H.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravascular use |

Dosage and administration details:

500 mg/m² via IV infusion on Day 1 of every 2-week cycle

| | |
|--|--|
| Investigational medicinal product name | Fluoropyrimidine (5-FU/LV or capecitabine) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m² administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m² administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m² twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen

fluoropyrimidine should be administered in accordance with local prescribing information.

| | |
|--|-----------------------|
| Investigational medicinal product name | 5-FU/LV |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1600-2400 mg/m² 5-FU via 46-hour IV infusion in combination with 400 mg/m² LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression per the Investigator's assessment using modified Response Evaluation Criteria in Solid Tumors or death from any cause, whichever occurs first.

| | |
|--|---|
| Investigational medicinal product name | Vemurafenib |
| Investigational medicinal product code | |
| Other name | RO5185426 |
| Pharmaceutical forms | Solution for infusion, Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

960 mg vemurafenib BID by mouth

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

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

Dosage and administration details:

800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle, or a fixed dose of 840 mg

| Number of subjects in period 3 ^[2] | Early Progressing BRAFmut Cohort |
|--|-------------------------------------|
| | Started |
| Completed | 0 |
| Not completed | 11 |
| Death | 10 |
| Lost to follow-up | 1 |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: BRAFmut participants experiencing early disease progression during induction treatment had the option of proceeding immediately to receive second-line treatment. These participants are presented in a separate arm in a separate period as they were not considered part of Maintenance Treatment.

Baseline characteristics

Reporting groups

| | |
|---|--------------------------------|
| Reporting group title | Cohort 1: Induction Phase (IP) |
| Reporting group description: | |
| Included participants with v-raf murine sarcoma viral oncogene homolog B1 mutation positive (BRAFmut)/human epidermal growth factor receptor 2 negative (HER2-)/microsatellite stable (MSS)/rat sarcoma wild type (RASwt). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment. | |
| Reporting group title | Cohort 2 (IP) |
| Reporting group description: | |
| Included participants with BRAFwt. All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment. | |
| Reporting group title | Cohort 3 (IP) |
| Reporting group description: | |
| Included participants with human epidermal growth factor receptor 2 positive (HER2+). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment. | |
| Reporting group title | Cohort 4 (IP) |
| Reporting group description: | |
| Included participants with HER2-/high microsatellite instability (MSI-H); HER2-/MSS/v-raf murine sarcoma viral oncogene homolog B1 wild type (BRAFwt); HER2-/MSS/BRAFmut/rat sarcoma mutation positive (RASmut). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment. | |

| Reporting group values | Cohort 1: Induction Phase (IP) | Cohort 2 (IP) | Cohort 3 (IP) |
|--|--------------------------------|---------------|---------------|
| Number of subjects | 93 | 635 | 6 |
| 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) | 58 | 351 | 6 |
| From 65-84 years | 35 | 279 | 0 |
| 85 years and over | 0 | 5 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 59.5 | 60.9 | 48.0 |
| standard deviation | ± 12.0 | ± 12.6 | ± 7.7 |

| | | | |
|-------------------|----|-----|---|
| Sex: Female, Male | | | |
| Units: | | | |
| Female | 49 | 247 | 4 |
| Male | 44 | 388 | 2 |

| Reporting group values | Cohort 4 (IP) | Total | |
|---|---------------|-------|--|
| Number of subjects | 310 | 1044 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 199 | 614 | |
| From 65-84 years | 110 | 424 | |
| 85 years and over | 1 | 6 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.1 | | |
| standard deviation | ± 10.3 | - | |
| Sex: Female, Male | | | |
| Units: | | | |
| Female | 123 | 423 | |
| Male | 187 | 621 | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Cohort 1: Induction Phase (IP) |
| Reporting group description: Included participants with v-raf murine sarcoma viral oncogene homolog B1 mutation positive (BRAFmut)/human epidermal growth factor receptor 2 negative (HER2-)/microsatellite stable (MSS)/rat sarcoma wild type (RASwt). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment. | |
| Reporting group title | Cohort 2 (IP) |
| Reporting group description: Included participants with BRAFwt. All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment. | |
| Reporting group title | Cohort 3 (IP) |
| Reporting group description: Included participants with human epidermal growth factor receptor 2 positive (HER2+). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment. | |
| Reporting group title | Cohort 4 (IP) |
| Reporting group description: Included participants with HER2-/high microsatellite instability (MSI-H); HER2-/MSS/v-raf murine sarcoma viral oncogene homolog B1 wild type (BRAFwt); HER2-/MSS/BRAFmut/rat sarcoma mutation positive (RASmut). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment. | |
| Reporting group title | Cohort 1: 5-FU/LV,cetuximab,vemurafenib |
| Reporting group description: Participants with v-raf murine sarcoma viral oncogene homolog B1 mutation positive (BRAFmut)/human epidermal growth factor receptor 2 negative (HER2-)/microsatellite stable (MSS)/rat sarcoma wild type (RASwt) received 1600-2400 milligrams per square meter (mg/m ²) 5-FU via 46-hour intravenous (IV) infusion in combination with 400 mg/m ² LV via 2-hour infusion on Day 1 of every 2-week cycle with 500 mg/m ² cetuximab via infusion on Day 1 of every 2-week cycle and 960 milligrams (mg) vemurafenib twice daily (BID) by mouth. | |
| Reporting group title | Cohort 1 Control: 5-FU/LV or capecitabine, bevacizumab |
| Reporting group description: Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle. | |
| Reporting group title | Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab |
| Reporting group description: Participants with BRAFwt received fluoropyrimidine (1600-2400 mg/m ² 5-FU via 46-hour IV infusion in combination with 400 mg/m ² LV via 2-hour infusion on Day 1 of every 2-week cycle or 1000 mg/m ² twice-daily capecitabine BID by mouth on Days 1-14 every 2 weeks followed by a 1-week break) with 5 milligrams per kilogram (mg/kg) bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle and 800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle. | |
| Reporting group title | Cohort 2 Control: 5-FU/LV or capecitabine, bevacizumab |
| Reporting group description: Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle. | |
| Reporting group title | Cohort 3: capecitabine,trastuzumab,pertuzumab |

Reporting group description:

Participants with human epidermal growth factor receptor 2 positive (HER2+) received 1000 mg/m² twice-daily capecitabine BID by mouth on Days 1-14 every 2 weeks followed by a 1-week break with trastuzumab by IV infusion on Day 1 of every 3-week treatment cycle at an initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses, and pertuzumab by IV infusion on Day 1 of each 3-week treatment cycle at an initial fixed loading dose of 840 mg followed by 420 mg for subsequent doses.

| | |
|-----------------------|---|
| Reporting group title | Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab |
|-----------------------|---|

Reporting group description:

Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Cohort 4: Cobimetinib,atezolizumab |
|-----------------------|------------------------------------|

Reporting group description:

Participants with HER2-/high microsatellite instability (MSI-H); HER2-/MSS/v-raf murine sarcoma viral oncogene homolog B1 wild type (BRAFWt); HER2-/MSS/BRAFmut/rat sarcoma mutation positive (RASmut) received 60 mg cobimetinib orally for 3 weeks followed by a 1-week treatment break and atezolizumab at a fixed dose of 840 mg via 60-minute IV infusion on Day 1 of every 2-week cycle.

| | |
|-----------------------|---|
| Reporting group title | Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab |
|-----------------------|---|

Reporting group description:

Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Early Progressing BRAFmut Cohort |
|-----------------------|----------------------------------|

Reporting group description:

BRAFmut participants experiencing early disease progression during induction treatment had the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib if their primary tumour was MSS, or with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab if their primary tumour was MSI-H.

Primary: Progression-Free Survival

| | |
|-----------------|---------------------------|
| End point title | Progression-Free Survival |
|-----------------|---------------------------|

End point description:

PFS is defined as the time from randomization to the first occurrence of disease progression according to RECIST v1.1, or death from any cause, whichever occurs first. Progressive disease (PD) for target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥5 mm. PD for non-target lesion: Unequivocal progression of existing non-target lesions. Analysis Population included participants in the Maintenance Treatment Phase (MTP) of the study, which included the experimental and control arms of Cohorts 1-4.

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

End point timeframe:

From randomization until disease progression or death from any cause, up to 5 years

| End point values | Cohort 1: 5-FU/LV,cetuximab,vemurafenib | Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab | Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab |
|----------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 20 | 297 | 148 |
| Units: months | | | | |
| median (confidence interval 95%) | 9.99 (7.72 to | 11.60 (3.58 to | 7.13 (6.14 to | 7.36 (5.82 to |

| | | | |
|--------|--------|-------|-------|
| 12.55) | 15.67) | 8.41) | 8.94) |
|--------|--------|-------|-------|

| End point values | Cohort 3: capecitabine, tr astuzumab, per tuzumab | Cohort 3 Control: 5- FU/LV or capecitabin, bevacizumab | Cohort 4: Cobimetinib, at ezolizumab | Cohort 4 Control: 5- FU/LV or capecitabin, bevacizumab |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 2 | 65 | 34 |
| Units: months | | | | |
| median (confidence interval 95%) | 4.44 (3.55 to 14.69) | 4.04 (4.04 to 5.39) | 3.75 (3.42 to 3.91) | 7.79 (3.98 to 9.46) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | MTP: Cohort 1 vs Cohort 1 Control |
| Comparison groups | Cohort 1: 5-FU/LV, cetuximab, vemurafenib v Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.872 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.82 |

| | |
|---|---|
| Statistical analysis title | MTP: Cohort 4 vs Cohort 4 Control |
| Comparison groups | Cohort 4: Cobimetinib, atezolizumab v Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.128 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 2.29 |

| | |
|---|--|
| Statistical analysis title | MTP: Cohort 2 vs Cohort 2 Control |
| Comparison groups | Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab v Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.666 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.18 |

Secondary: Overall Survival

| | |
|------------------------|--|
| End point title | Overall Survival |
| End point description: | OS is defined as the time from randomization into the MTP to time of death from any cause. Analysis Population included participants in the MTP of the study, which included the experimental and control arms of Cohorts 1-4. |
| End point type | Secondary |
| End point timeframe: | From randomization until death from any cause, up to 5 years |

| End point values | Cohort 1: 5-FU/LV, cetuximab, vemurafenib | Early Progressing BRAFmut Cohort | Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 2: 5-FU/LV or capecitabine, bevacizumab, atezolizumab |
|----------------------------------|---|----------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 11 | 20 | 297 |
| Units: months | | | | |
| median (confidence interval 95%) | 24.02 (16.07 to 34.00) | 10.51 (4.83 to 19.78) | 21.73 (7.92 to 37.19) | 22.54 (20.04 to 26.87) |

| End point values | Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 3: capecitabine, trastuzumab, pertuzumab | Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 4: Cobimetinib, atezolizumab |
|-------------------------|---|---|---|-------------------------------------|
| | | | | |

| | | | | |
|----------------------------------|------------------------|------------------|------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 148 | 0 ^[1] | 0 ^[2] | 65 |
| Units: months | | | | |
| median (confidence interval 95%) | 22.24 (18.50 to 25.13) | (to) | (to) | 22.60 (14.23 to 27.40) |

Notes:

[1] - Both the Median and the 95% CI were not evaluable due to the low number of participants/events.

[2] - Both the Median and the 95% CI were not evaluable due to the low number of participants/events.

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 25.17 (15.90 to 32.59) | | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | MTP: Cohort 1 vs Cohort 1 Control |
| Comparison groups | Cohort 1: 5-FU/LV,cetuximab,vemurafenib v Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.276 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 1.32 |

| | |
|---|--|
| Statistical analysis title | MTP: Cohort 4 vs Cohort 4 Control |
| Comparison groups | Cohort 4: Cobimetinib,atezolizumab v Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.415 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.25 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 2.14 |

| | |
|---|--|
| Statistical analysis title | MTP: Cohort 2 vs Cohort 2 Control |
| Comparison groups | Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab v Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.076 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.02 |

Secondary: Percentage of Participants with Adverse Events

| | |
|------------------------|--|
| End point title | Percentage of Participants with Adverse Events |
| End point description: | Safety population: all participants who received an intervention during the study. |
| End point type | Secondary |
| End point timeframe: | From baseline until end of study (up to 5 years) |

| End point values | Cohort 1: Induction Phase (IP) | Cohort 1: 5- FU/LV,cetuxim ab,vemurafenib | Early Progressing BRAFmut Cohort | Cohort 2 (IP) |
|-----------------------------------|--------------------------------------|---|---|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 93 | 40 | 11 | 632 |
| Units: percentage of participants | | | | |
| number (not applicable) | 98.9 | 100 | 90.9 | 96.0 |

| End point values | Cohort 1 Control: 5- FU/LV or capecitabin, | Cohort 3 (IP) | Cohort 2: 5- FU/LV or capecitabine,be vacizumab, | Cohort 4 (IP) |
|-------------------------|---|---------------|---|---------------|
| | | | | |

| | bevacizumab | | atezolizumab | |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 | 6 | 293 | 309 |
| Units: percentage of participants | | | | |
| number (not applicable) | 94.4 | 100 | 95.6 | 97.4 |

| End point values | Cohort 2 Control: 5- FU/LV or capecitabin, bevacizumab | Cohort 3: capecitabine, tr astuzumab, per tuzumab | Cohort 3 Control: 5- FU/LV or capecitabin, bevacizumab | Cohort 4: Cobimetinib, at ezolizumab |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 143 | 3 | 2 | 64 |
| Units: percentage of participants | | | | |
| number (not applicable) | 88.1 | 100 | 100 | 98.4 |

| End point values | Cohort 4 Control: 5- FU/LV or capecitabin, bevacizumab | | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 88.2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response

| | |
|------------------------|--|
| End point title | Overall Response |
| End point description: | Calculated as the number of participants with a best overall response of CR or PR according to RECIST 1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. OR= CR + PR. Analysis Population included participants in the MTP of the study, which included the experimental and control arms of Cohorts 1-4. |
| End point type | Secondary |
| End point timeframe: | From randomization until disease progression, up to 5 years |

| | | | | |
|-----------------------------|---|----------------------------------|---|--|
| End point values | Cohort 1: 5-FU/LV, cetuximab, vemurafenib | Early Progressing BRAFmut Cohort | Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 2: 5-FU/LV or capecitabine, bevacizumab, atezolizumab |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 11 | 20 | 297 |
| Units: participants | 20 | 2 | 5 | 49 |

| | | | | |
|-----------------------------|---|---|---|-------------------------------------|
| End point values | Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 3: capecitabine, trastuzumab, pertuzumab | Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 4: Cobimetinib, atezolizumab |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 148 | 3 | 2 | 65 |
| Units: participants | 22 | 1 | 0 | 7 |

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: participants | 8 | | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | MTP: Cohort 1 vs Cohort 1 Control |
| Comparison groups | Cohort 1: 5-FU/LV, cetuximab, vemurafenib v Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.064 |
| Method | Chi-squared |

| | |
|-----------------------------------|---|
| Statistical analysis title | MTP: Cohort 4 vs Cohort 4 Control |
| Comparison groups | Cohort 4: Cobimetinib, atezolizumab v Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab |

| | |
|---|---------------|
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.093 |
| Method | Chi-squared |

| | |
|---|--|
| Statistical analysis title | MTP: Cohort 2 vs Cohort 2 Control |
| Comparison groups | Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab v Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.658 |
| Method | Chi-squared |

Secondary: Disease Control Rate

| | |
|---|----------------------|
| End point title | Disease Control Rate |
| End point description: | |
| DCR is defined as the percentage of participants with CR, PR, or stable disease (SD) at 16 weeks. Per RECIST v1.1, CR is defined as disappearance of all target lesions. PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression, taking as reference the smallest sum on study. Disease progression is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline, or the appearance of one or more new lesions. Analysis Population included participants in the MTP of the study, which included the experimental and control arms of Cohorts 1-4. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until disease progression, up to 5 years | |

| End point values | Cohort 1: 5-FU/LV, cetuximab, vemurafenib | Early Progressing BRAFmut Cohort | Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 2: 5-FU/LV or capecitabine, bevacizumab, atezolizumab |
|-----------------------------|---|----------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 11 | 20 | 297 |
| Units: participants | 36 | 9 | 15 | 227 |

| End point values | Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 3: capecitabine, trastuzumab, perituzumab | Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 4: Cobimetinib, atezolizumab |
|-------------------------|---|--|---|-------------------------------------|
|-------------------------|---|--|---|-------------------------------------|

| | | | | |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 148 | 3 | 2 | 65 |
| Units: participants | 111 | 1 | 0 | 44 |

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: participants | 26 | | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | MTP: Cohort 1 vs Cohort 1 Control |
| Comparison groups | Cohort 1: 5-FU/LV, cetuximab, vemurafenib v Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.125 |
| Method | Chi-squared |

| | |
|---|---|
| Statistical analysis title | MTP: Cohort 4 vs Cohort 4 Control |
| Comparison groups | Cohort 4: Cobimetinib, atezolizumab v Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.362 |
| Method | Chi-squared |

| | |
|---|--|
| Statistical analysis title | MTP: Cohort 2 vs Cohort 2 Control |
| Comparison groups | Cohort 2: 5-FU/LV or capecitabine, bevacizumab, atezolizumab v Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.739 |
| Method | Chi-squared |

Secondary: Duration of Response

| | |
|---|----------------------|
| End point title | Duration of Response |
| End point description: | |
| Defined as the time from the first assessment of CR or PR until disease progression or death from any cause, whichever occurs first. CR is defined as disappearance of all target lesions. PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Analysis Population included participants in the MTP of the study, which included the experimental and control arms of Cohorts 1-4. | |
| End point type | Secondary |
| End point timeframe: | |
| From first objective response until disease progression or death from any cause, up to 5 years | |

| End point values | Cohort 1: 5-FU/LV, cetuximab, vemurafenib | Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 2: 5-FU/LV or capecitabine, bevacizumab, atezolizumab | Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab |
|----------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 20 | 297 | 148 |
| Units: months | | | | |
| median (confidence interval 95%) | 11.50 (7.66 to 21.49) | 8.74 (5.36 to 19.02) | 9.30 (5.55 to 11.30) | 7.59 (6.93 to 13.90) |

| End point values | Cohort 3: capecitabine, trastuzumab, pertuzumab | Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 4: Cobimetinib, atezolizumab | Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab |
|----------------------------------|---|---|-------------------------------------|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 2 | 0 ^[3] | 0 ^[4] |
| Units: months | | | | |
| median (confidence interval 95%) | 9.205 (9.205 to 9.205) | 0 (0 to 0) | (to) | (to) |

Notes:

[3] - Target number of patients not enrolled and the target number of PFS events could not be reached

[4] - Target number of patients not enrolled and the target number of PFS events could not be reached

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | MTP: Cohort 2 vs Cohort 2 Control |
| Comparison groups | Cohort 2: 5-FU/LV or capecitabine, bevacizumab, atezolizumab v Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab |

| | |
|---|---------------|
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.495 |
| Method | Logrank |

| | |
|---|---|
| Statistical analysis title | MTP: Cohort 1 vs Cohort 1 Control |
| Comparison groups | Cohort 1: 5-FU/LV,cetuximab,vemurafenib v Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.421 |
| Method | Logrank |

Secondary: Time to Treatment Response

| | |
|------------------------|--|
| End point title | Time to Treatment Response |
| End point description: | Calculated as the time from randomization to the first Occurrence of a documented Objective Response (CR or PR) determined according to RECIST 1.1. CR is defined as disappearance of all target lesions. PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Analysis Population included participants in the MTP of the study, which included the experimental and control arms of Cohorts 1-4. |
| End point type | Secondary |
| End point timeframe: | From randomization until disease progression or death from any cause, up to 5 years |

| End point values | Cohort 1: 5-FU/LV,cetuximab,vemurafenib | Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab | Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab |
|-------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 20 | 297 | 148 |
| Units: months | | | | |
| median (full range (min-max)) | 3.943 (1.18 to 29.70) | 5.552 (1.38 to 8.02) | 5.224 (1.22 to 26.74) | 4.616 (1.25 to 19.91) |

| End point values | Cohort 3: capecitabine, trastuzumab, pertuzumab | Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab | Cohort 4: Cobimetinib, atezolizumab | Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab |
|-----------------------------|---|---|-------------------------------------|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 2 | 0 ^[5] | 0 ^[6] |

| | | | | |
|-------------------------------|------------------------|------------|--------|--------|
| Units: months | | | | |
| median (full range (min-max)) | 5.490 (5.490 to 5.490) | 0 (0 to 0) | (to) | (to) |

Notes:

[5] - Target number of patients not enrolled and the target number of PFS events could not be reached

[6] - Target number of patients not enrolled and the target number of PFS events could not be reached

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Improvement and/or Stayed the Same on the Eastern Cooperative Oncology Group Performance Status (ECOG PS) Score

| | |
|-----------------|---|
| End point title | Percentage of Participants With Improvement and/or Stayed the Same on the Eastern Cooperative Oncology Group Performance Status (ECOG PS) Score |
|-----------------|---|

End point description:

Analysis Population included participants in the MTP of the study, which included the experimental and control arms of Cohorts 1-4.

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

End point timeframe:

From baseline until end of study (up to 5 years)

| End point values | Cohort 1: 5-FU/LV, cetuximab, vemurafenib | Cohort 1 Control: 5-FU/LV or capecitabine, bevacizumab | Cohort 2: 5-FU/LV or capecitabine, bevacizumab, atezolizumab | Cohort 2 Control: 5-FU/LV or capecitabine, bevacizumab |
|-----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 20 | 297 | 148 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Improved | 10.0 | 5.0 | 10.4 | 5.4 |
| Improved or stayed the same | 75.0 | 85.0 | 76.7 | 82.5 |

| End point values | Cohort 3: capecitabine, trastuzumab, pertuzumab | Cohort 3 Control: 5-FU/LV or capecitabine, bevacizumab | Cohort 4: Cobimetinib, atezolizumab | Cohort 4 Control: 5-FU/LV or capecitabine, bevacizumab |
|-----------------------------------|---|--|-------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 2 | 65 | 34 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Improved | 0 | 0 | 7.7 | 5.9 |
| Improved or stayed the same | 100 | 100 | 63.1 | 79.4 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline until end of study (up to 5 years)

Adverse event reporting additional description:

The safety population included all participants who received an intervention during the study.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Cohort 1: Induction Phase (IP) |
|-----------------------|--------------------------------|

Reporting group description:

Included participants with v-raf murine sarcoma viral oncogene homolog B1 mutation positive (BRAFmut)/human epidermal growth factor receptor 2 negative (HER2-)/microsatellite stable (MSS)/rat sarcoma wild type (RASwt). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment.

| | |
|-----------------------|---|
| Reporting group title | Cohort 1 Control (MP): 5-FU/LV or capecitabine, bevacizumab |
|-----------------------|---|

Reporting group description:

Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

| | |
|-----------------------|---------------|
| Reporting group title | Cohort 2 (IP) |
|-----------------------|---------------|

Reporting group description:

Included participants with BRAFwt. All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2 (MP):5-FU/LV or capecitabine,bevacizumab,atezolizumab |
|-----------------------|--|

Reporting group description:

Participants with BRAFwt received fluoropyrimidine (1600-2400 mg/m² 5-FU via 46-hour IV infusion in combination with 400 mg/m² LV via 2-hour infusion on Day 1 of every 2-week cycle or 1000 mg/m² twice-daily capecitabine BID by mouth on Days 1-14 every 2 weeks followed by a 1-week break) with 5 milligrams per kilogram (mg/kg) bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle and 800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle.

| | |
|-----------------------|---|
| Reporting group title | Cohort 2 Control (MP): 5-FU/LV or capecitabine, bevacizumab |
|-----------------------|---|

Reporting group description:

Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Early Progressing BRAFmut Cohort |
|-----------------------|----------------------------------|

Reporting group description:

BRAFmut participants experiencing early disease progression during induction treatment had the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib if their primary tumor was MSS, or with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab if their primary tumor was MSI-H. This cohort was followed during the study, but was not part of the Maintenance Phase study objectives.

| | |
|-----------------------|--|
| Reporting group title | Cohort 3 (MP): capecitabine,trastuzumab,pertuzumab |
|-----------------------|--|

Reporting group description:

Participants with human epidermal growth factor receptor 2 positive (HER2+) received 1000 mg/m² twice-daily capecitabine BID by mouth on Days 1-14 every 2 weeks followed by a 1-week break with trastuzumab by IV infusion on Day 1 of every 3-week treatment cycle at an initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses, and pertuzumab by IV infusion on Day 1 of each 3-

week treatment cycle at an initial fixed loading dose of 840 mg followed by 420 mg for subsequent doses.

| | |
|-----------------------|--|
| Reporting group title | Cohort 3 Control (MP): 5-FU/LV or capecitabin, bevacizumab |
|-----------------------|--|

Reporting group description:

Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

| | |
|-----------------------|---------------|
| Reporting group title | Cohort 4 (IP) |
|-----------------------|---------------|

Reporting group description:

Included participants with HER2-/high microsatellite instability (MSI-H); HER2-/MSS/v-raf murine sarcoma viral oncogene homolog B1 wild type (BRAFWt); HER2-/MSS/BRAFmut/rat sarcoma mutation positive (RASmut). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment.

| | |
|-----------------------|---|
| Reporting group title | Cohort 4 (MP): Cobimetinib,atezolizumab |
|-----------------------|---|

Reporting group description:

Participants with HER2-/high microsatellite instability (MSI-H); HER2-/MSS/v-raf murine sarcoma viral oncogene homolog B1 wild type (BRAFWt); HER2-/MSS/BRAFmut/rat sarcoma mutation positive (RASmut) received 60 mg cobimetinib orally for 3 weeks followed by a 1-week treatment break and atezolizumab at a fixed dose of 840 mg via 60-minute IV infusion on Day 1 of every 2-week cycle.

| | |
|-----------------------|--|
| Reporting group title | Cohort 4 Control (MP): 5-FU/LV or capecitabin, bevacizumab |
|-----------------------|--|

Reporting group description:

Per Investigator discretion, participants received fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

| | |
|-----------------------|--|
| Reporting group title | Cohort 1 (Maintenance Phase[MP]):5-FU/LV,cetuximab,vemurafenib |
|-----------------------|--|

Reporting group description:

Participants with v-raf murine sarcoma viral oncogene homolog B1 mutation positive (BRAFMut)/human epidermal growth factor receptor 2 negative (HER2-)/microsatellite stable (MSS)/rat sarcoma wild type (RASwt) received 1600-2400 milligrams per square meter (mg/m²) 5-FU via 46-hour intravenous (IV) infusion in combination with 400 mg/m² LV via 2-hour infusion on Day 1 of every 2-week cycle with 500 mg/m² cetuximab via infusion on Day 1 of every 2-week cycle and 960 milligrams (mg) vemurafenib twice daily (BID) by mouth.

| | |
|-----------------------|---------------|
| Reporting group title | Cohort 3 (IP) |
|-----------------------|---------------|

Reporting group description:

Included participants with human epidermal growth factor receptor 2 positive (HER2+). All study participants received either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab during Induction Treatment.

| Serious adverse events | Cohort 1: Induction Phase (IP) | Cohort 1 Control (MP): 5-FU/LV or capecitabin, bevacizumab | Cohort 2 (IP) |
|---|--------------------------------|--|--------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 44 / 93 (47.31%) | 5 / 18 (27.78%) | 232 / 632 (36.71%) |
| number of deaths (all causes) | 25 | 16 | 111 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Second primary malignancy | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour perforation | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leiomyosarcoma | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine tumour | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Arterial thrombosis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 6 / 632 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 6 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dry gangrene | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Embolism venous | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Ureteral stent removal | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site dehiscence | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|------------------|
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 6 / 632 (0.95%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site thrombosis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 14 / 632 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 4 / 15 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| Euthanasia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related hypersensitivity reaction | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 7 / 632 (1.11%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 6 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hypoventilation | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|-----------------|
| Blood triglycerides increased subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amylase increased subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza A virus test positive subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications Anastomotic ulcer subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|-----------------|
| Femur fracture | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incisional hernia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheal haemorrhage | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal anastomotic leak | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incision site impaired healing | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative thoracic procedure complication | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Restrictive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reversible cerebral vasoconstriction syndrome | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiplegia | | | |

| | | | |
|---|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 10 / 632 (1.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 13 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 12 / 632 (1.90%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 11 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic haematoma | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |

| | | | |
|---|----------------|----------------|-----------------|
| Vertigo | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Choroidal effusion | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 4 / 632 (0.63%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 7 / 632 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|------------------|
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 1 / 18 (5.56%) | 13 / 632 (2.06%) |
| occurrences causally related to treatment / all | 4 / 5 | 1 / 1 | 9 / 14 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 1 / 18 (5.56%) | 10 / 632 (1.58%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 3 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 4 / 632 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 5 / 632 (0.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| Large intestinal stenosis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 5 / 632 (0.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |

| | | | |
|---|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 4 / 632 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 10 / 632 (1.58%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 6 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colonic fistula | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis mesenteric vessel | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal perforation | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal perforation | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 93 (2.15%) | 1 / 18 (5.56%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatorenal failure | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraneoplastic dermatomyositis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 5 / 632 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|-----------------|
| Bone pain | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal infection | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 1 / 18 (5.56%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 93 (2.15%) | 1 / 18 (5.56%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gingivitis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic infection | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Labyrinthitis | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine infection | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 8 / 632 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 4 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 6 / 632 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 8 / 632 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 6 / 632 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural sepsis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fournier's gangrene | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary infection | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic abscess | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral discitis | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort 2 (MP):5-FU/LV or capecitabine,bevacizumab,atezolizumab | Cohort 2 Control (MP): 5-FU/LV or capecitabin, bevacizumab | Early Progressing BRAFmut Cohort |
|--|--|--|----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 76 / 293 (25.94%) | 20 / 143 (13.99%) | 3 / 11 (27.27%) |
| number of deaths (all causes) | 185 | 102 | 10 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Second primary malignancy | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour perforation | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leiomyosarcoma | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine tumour | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Arterial thrombosis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 3 / 293 (1.02%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dry gangrene | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism venous | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Ureteral stent removal | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site dehiscence | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site thrombosis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 293 (2.05%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Euthanasia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related hypersensitivity reaction | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoventilation | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| Amylase increased | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza A virus test positive | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Anastomotic ulcer | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incisional hernia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheal haemorrhage | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal anastomotic leak | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incision site impaired healing | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative thoracic procedure complication | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Restrictive cardiomyopathy | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac tamponade | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reversible cerebral vasoconstriction syndrome | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic haematoma | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Choroidal effusion | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 3 / 293 (1.02%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 293 (1.71%) | 2 / 143 (1.40%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 3 / 5 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Large intestinal stenosis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 4 / 293 (1.37%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colonic fistula | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis mesenteric vessel | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal perforation | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal perforation | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Hepatocellular injury | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatorenal failure | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palmar-plantar erythrodysesthesia syndrome | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraneoplastic dermatomyositis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| Abdominal infection | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic infection | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Labyrinthitis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine infection | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal abscess | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 293 (1.02%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural sepsis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fournier's gangrene | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary infection | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic abscess | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomembranous colitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort 3 (MP): capecitabine, trastuzumab, pertuzumab | Cohort 3 Control (MP): 5-FU/LV or capecitabine, bevacizumab | Cohort 4 (IP) |
|---|---|---|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 93 / 309 (30.10%) |
| number of deaths (all causes) | 1 | 1 | 82 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Second primary malignancy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour perforation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leiomyosarcoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine tumour | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Arterial thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dry gangrene | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism venous | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Ureteral stent removal | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|---------------|-----------------|
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site dehiscence | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 8 / 309 (2.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |

| | | | |
|--|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Euthanasia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related hypersensitivity reaction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---------------|---------------|-----------------|
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory distress syndrome | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoventilation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |

| | | | |
|---|---------------|---------------|-----------------|
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza A virus test positive | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Anastomotic ulcer | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incisional hernia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal anastomotic leak | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incision site impaired healing | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative thoracic procedure complication | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Restrictive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reversible cerebral vasoconstriction syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 4 / 309 (1.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic haematoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Choroidal effusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 6 / 309 (1.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|---------------|-----------------|
| Colitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 4 / 309 (1.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Intestinal obstruction | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 4 / 309 (1.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal stenosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctalgia | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colonic fistula | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis mesenteric vessel | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Small intestinal perforation | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal perforation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatorenal failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraneoplastic dermatomyositis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 8 / 309 (2.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 6 / 11 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |

| | | | |
|---|---------------|---------------|-----------------|
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|---------------|-----------------|
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis infective | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Labyrinthitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 4 / 309 (1.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural sepsis | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fournier's gangrene | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic abscess | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |

| | | | |
|---|---------------|---------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort 4 (MP): Cobimetinib,atezoliz umab | Cohort 4 Control (MP): 5-FU/LV or capecitabin, bevacizumab | Cohort 1 (Maintenance Phase[MP]):5- FU/LV,cetuximab,ve murafenib |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 26 / 64 (40.63%) | 3 / 34 (8.82%) | 15 / 40 (37.50%) |
| number of deaths (all causes) | 46 | 19 | 29 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Second primary malignancy | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour perforation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leiomyosarcoma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine tumour | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Arterial thrombosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dry gangrene | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism venous | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Ureteral stent removal | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site dehiscence | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site thrombosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Euthanasia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related hypersensitivity reaction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Organising pneumonia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoventilation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza A virus test positive | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Anastomotic ulcer | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Femur fracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incisional hernia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheal haemorrhage | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal anastomotic leak | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incision site impaired healing | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative thoracic procedure complication | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Restrictive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 34 (2.94%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reversible cerebral vasoconstriction syndrome | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiplegia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic haematoma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Vertigo | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Choroidal effusion | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 1 / 34 (2.94%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal stenosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colonic fistula | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis mesenteric vessel | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal perforation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal perforation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatorenal failure | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraneoplastic dermatomyositis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 34 (2.94%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 34 (2.94%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Bone pain | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Labyrinthitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine infection | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural sepsis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fournier's gangrene | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic abscess | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral discitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort 3 (IP) | | |
|--|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Second primary malignancy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour perforation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---------------|--|--|
| Leiomyosarcoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuroendocrine tumour | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Arterial thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superior vena cava syndrome | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dry gangrene | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism venous | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Ureteral stent removal | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |

| | | | | |
|---|---------------|--|--|--|
| Asthenia | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chest pain | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gait disturbance | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fatigue | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Implant site dehiscence | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hyperthermia | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Implant site thrombosis | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infusion site extravasation | | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Euthanasia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypersensitivity | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infusion related hypersensitivity reaction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---------------|--|--|
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoventilation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |

| | | | |
|---|---------------|--|--|
| Disorientation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|---------------|--|--|
| Hepatic enzyme increased subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza A virus test positive subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelet count decreased subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Anastomotic ulcer subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Incisional hernia subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haemorrhage subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal fracture subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|---------------|--|--|--|
| Rib fracture | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Stoma site haemorrhage | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tendon rupture | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tibia fracture | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tracheal haemorrhage | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pelvic fracture | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fall | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femoral neck fracture | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal anastomotic leak | | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Incision site impaired healing | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative thoracic procedure complication | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiogenic shock | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Restrictive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial thrombosis | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reversible cerebral vasoconstriction syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Splenic haematoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Chorioretinopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Choroidal effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

| | | | | |
|---|---------------|--|--|--|
| Abdominal pain | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal pain upper | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Constipation | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Faecaloma | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal obstruction | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroesophageal reflux disease | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ileus | | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestinal stenosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subileus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colonic fistula | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoidal haemorrhage | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis mesenteric vessel | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal perforation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal perforation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatorenal failure | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Paraneoplastic dermatomyositis | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|---------------|--|--|
| disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fistula | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|---------------|--|--|--|
| Abdominal wall abscess | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anal abscess | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arthritis infective | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchitis | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Device related infection | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulitis | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Erysipelas | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gingivitis | | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Labyrinthitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fournier's gangrene | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious pleural effusion | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic abscess | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pilonidal cyst | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Cohort 1: Induction Phase (IP) | Cohort 1 Control (MP): 5-FU/LV or capecitabin, bevacizumab | Cohort 2 (IP) |
|--|--------------------------------|--|--------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 91 / 93 (97.85%) | 17 / 18 (94.44%) | 608 / 632 (96.20%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences (all) | 1 | 0 | 1 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 5 / 632 (0.79%) |
| occurrences (all) | 0 | 0 | 5 |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 16 / 93 (17.20%) | 1 / 18 (5.56%) | 170 / 632 (26.90%) |
| occurrences (all) | 21 | 1 | 244 |
| Hypotension | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | 0 / 18 (0.00%) | 10 / 632 (1.58%) |
| occurrences (all) | 8 | 0 | 10 |
| Phlebitis | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 6 / 632 (0.95%) |
| occurrences (all) | 3 | 0 | 6 |
| General disorders and administration site conditions | | | |
| Face oedema | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences (all) | 0 | 0 | 5 |
| Asthenia | | | |
| subjects affected / exposed | 20 / 93 (21.51%) | 1 / 18 (5.56%) | 115 / 632 (18.20%) |
| occurrences (all) | 32 | 2 | 214 |
| Fatigue | | | |

| | | | |
|--|------------------------|----------------------|---------------------------|
| subjects affected / exposed occurrences (all) | 31 / 93 (33.33%) 50 | 2 / 18 (11.11%) 2 | 247 / 632 (39.08%) 403 |
| Influenza like illness subjects affected / exposed occurrences (all) | 5 / 93 (5.38%) 5 | 0 / 18 (0.00%) 0 | 21 / 632 (3.32%) 22 |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 16 / 93 (17.20%) 22 | 2 / 18 (11.11%) 4 | 69 / 632 (10.92%) 90 |
| Pain subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | 0 / 18 (0.00%) 0 | 16 / 632 (2.53%) 16 |
| Pyrexia subjects affected / exposed occurrences (all) | 19 / 93 (20.43%) 20 | 1 / 18 (5.56%) 1 | 93 / 632 (14.72%) 144 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 9 / 93 (9.68%) 13 | 0 / 18 (0.00%) 0 | 25 / 632 (3.96%) 25 |
| Catheter site pain subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 3 / 632 (0.47%) 4 |
| General physical health deterioration subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 2 | 0 / 18 (0.00%) 0 | 8 / 632 (1.27%) 8 |
| Malaise subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 2 | 0 / 18 (0.00%) 0 | 8 / 632 (1.27%) 9 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | 0 / 18 (0.00%) 0 | 15 / 632 (2.37%) 15 |
| Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 1 / 18 (5.56%) 1 | 3 / 632 (0.47%) 3 |
| Cough | | | |

| | | | |
|--|------------------------|----------------------|---------------------------|
| subjects affected / exposed occurrences (all) | 11 / 93 (11.83%) 12 | 3 / 18 (16.67%) 3 | 77 / 632 (12.18%) 95 |
| Dysphonia subjects affected / exposed occurrences (all) | 6 / 93 (6.45%) 7 | 1 / 18 (5.56%) 1 | 47 / 632 (7.44%) 61 |
| Dyspnoea subjects affected / exposed occurrences (all) | 8 / 93 (8.60%) 11 | 2 / 18 (11.11%) 2 | 47 / 632 (7.44%) 51 |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 6 / 93 (6.45%) 7 | 1 / 18 (5.56%) 1 | 19 / 632 (3.01%) 19 |
| Nasal ulcer subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 1 / 18 (5.56%) 1 | 0 / 632 (0.00%) 0 |
| Nasal dryness subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 3 | 1 / 18 (5.56%) 1 | 5 / 632 (0.79%) 5 |
| Epistaxis subjects affected / exposed occurrences (all) | 18 / 93 (19.35%) 24 | 1 / 18 (5.56%) 1 | 121 / 632 (19.15%) 157 |
| Hiccups subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 1 / 18 (5.56%) 1 | 20 / 632 (3.16%) 26 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 2 | 0 / 18 (0.00%) 0 | 20 / 632 (3.16%) 27 |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 6 / 93 (6.45%) 7 | 1 / 18 (5.56%) 1 | 19 / 632 (3.01%) 19 |
| Insomnia subjects affected / exposed occurrences (all) | 14 / 93 (15.05%) 14 | 1 / 18 (5.56%) 1 | 38 / 632 (6.01%) 40 |
| Depression subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | 0 / 18 (0.00%) 0 | 12 / 632 (1.90%) 13 |

| | | | |
|--|------------------|----------------|-------------------|
| Product issues | | | |
| Device occlusion | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences (all) | 3 | 0 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 0 / 18 (0.00%) | 34 / 632 (5.38%) |
| occurrences (all) | 7 | 0 | 52 |
| Amylase increased | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences (all) | 2 | 0 | 2 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | 1 / 18 (5.56%) | 35 / 632 (5.54%) |
| occurrences (all) | 9 | 1 | 45 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 19 / 632 (3.01%) |
| occurrences (all) | 3 | 0 | 20 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 0 / 18 (0.00%) | 13 / 632 (2.06%) |
| occurrences (all) | 8 | 0 | 19 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 1 / 18 (5.56%) | 18 / 632 (2.85%) |
| occurrences (all) | 6 | 1 | 24 |
| Lipase increased | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences (all) | 4 | 0 | 3 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 13 / 93 (13.98%) | 0 / 18 (0.00%) | 67 / 632 (10.60%) |
| occurrences (all) | 17 | 0 | 108 |
| Platelet count decreased | | | |

| | | | |
|--|------------------------|----------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 4 / 93 (4.30%) 7 | 0 / 18 (0.00%) 0 | 40 / 632 (6.33%) 74 |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 10 / 632 (1.58%) 11 |
| Weight decreased subjects affected / exposed occurrences (all) | 11 / 93 (11.83%) 12 | 2 / 18 (11.11%) 2 | 64 / 632 (10.13%) 69 |
| Cardiac murmur subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 0 / 632 (0.00%) 0 |
| Blood potassium decreased subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 1 / 632 (0.16%) 1 |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 7 / 632 (1.11%) 8 |
| Body temperature increased subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 0 / 632 (0.00%) 0 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 2 | 0 / 18 (0.00%) 0 | 16 / 632 (2.53%) 23 |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 7 / 632 (1.11%) 8 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction subjects affected / exposed occurrences (all) | 5 / 93 (5.38%) 6 | 0 / 18 (0.00%) 0 | 17 / 632 (2.69%) 28 |
| Lumbar vertebral fracture subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 1 / 632 (0.16%) 1 |
| Sunburn | | | |

| | | | |
|-------------------------------------|------------------|----------------|--------------------|
| subjects affected / exposed | 4 / 93 (4.30%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences (all) | 4 | 0 | 1 |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences (all) | 1 | 0 | 3 |
| Stoma site pain | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences (all) | 0 | 0 | 4 |
| Wound dehiscence | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 4 / 632 (0.63%) |
| occurrences (all) | 1 | 0 | 4 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | 1 / 18 (5.56%) | 29 / 632 (4.59%) |
| occurrences (all) | 11 | 2 | 35 |
| Dysgeusia | | | |
| subjects affected / exposed | 9 / 93 (9.68%) | 0 / 18 (0.00%) | 59 / 632 (9.34%) |
| occurrences (all) | 11 | 0 | 71 |
| Headache | | | |
| subjects affected / exposed | 7 / 93 (7.53%) | 0 / 18 (0.00%) | 73 / 632 (11.55%) |
| occurrences (all) | 10 | 0 | 179 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 0 / 18 (0.00%) | 10 / 632 (1.58%) |
| occurrences (all) | 5 | 0 | 11 |
| Neurotoxicity | | | |
| subjects affected / exposed | 9 / 93 (9.68%) | 0 / 18 (0.00%) | 22 / 632 (3.48%) |
| occurrences (all) | 15 | 0 | 31 |
| Paraesthesia | | | |
| subjects affected / exposed | 20 / 93 (21.51%) | 0 / 18 (0.00%) | 93 / 632 (14.72%) |
| occurrences (all) | 29 | 0 | 125 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 10 / 93 (10.75%) | 0 / 18 (0.00%) | 103 / 632 (16.30%) |
| occurrences (all) | 11 | 0 | 145 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 26 / 93 (27.96%) | 1 / 18 (5.56%) | 222 / 632 (35.13%) |
| occurrences (all) | 33 | 1 | 357 |

| | | | |
|--|------------------------|---------------------|---------------------------|
| Polyneuropathy subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | 1 / 18 (5.56%) 1 | 26 / 632 (4.11%) 35 |
| Restless legs syndrome subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | 1 / 18 (5.56%) 1 | 1 / 632 (0.16%) 1 |
| Somnolence subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | 0 / 18 (0.00%) 0 | 5 / 632 (0.79%) 7 |
| Taste disorder subjects affected / exposed occurrences (all) | 4 / 93 (4.30%) 4 | 0 / 18 (0.00%) 0 | 13 / 632 (2.06%) 13 |
| Sensory loss subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 2 | 1 / 18 (5.56%) 1 | 0 / 632 (0.00%) 0 |
| Ageusia subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 2 / 632 (0.32%) 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 20 / 93 (21.51%) 28 | 1 / 18 (5.56%) 2 | 87 / 632 (13.77%) 114 |
| Leukopenia subjects affected / exposed occurrences (all) | 5 / 93 (5.38%) 6 | 0 / 18 (0.00%) 0 | 40 / 632 (6.33%) 57 |
| Neutropenia subjects affected / exposed occurrences (all) | 22 / 93 (23.66%) 31 | 1 / 18 (5.56%) 1 | 133 / 632 (21.04%) 220 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 4 / 93 (4.30%) 5 | 0 / 18 (0.00%) 0 | 45 / 632 (7.12%) 67 |
| Ear and labyrinth disorders | | | |
| Auditory meatus external erosion subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 0 / 632 (0.00%) 0 |
| Eye disorders | | | |

| | | | |
|-----------------------------|------------------|-----------------|--------------------|
| Cataract | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences (all) | 5 | 0 | 4 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 2 / 632 (0.32%) |
| occurrences (all) | 1 | 1 | 2 |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 14 / 632 (2.22%) |
| occurrences (all) | 1 | 1 | 17 |
| Periorbital oedema | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 1 / 18 (5.56%) | 2 / 632 (0.32%) |
| occurrences (all) | 3 | 1 | 2 |
| Dry eye | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 0 / 18 (0.00%) | 5 / 632 (0.79%) |
| occurrences (all) | 3 | 0 | 5 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 7 / 632 (1.11%) |
| occurrences (all) | 1 | 0 | 7 |
| Gastrointestinal disorders | | | |
| Angular cheilitis | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 1 / 18 (5.56%) | 2 / 632 (0.32%) |
| occurrences (all) | 3 | 1 | 2 |
| Abdominal pain | | | |
| subjects affected / exposed | 28 / 93 (30.11%) | 1 / 18 (5.56%) | 113 / 632 (17.88%) |
| occurrences (all) | 34 | 1 | 152 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 12 / 93 (12.90%) | 3 / 18 (16.67%) | 56 / 632 (8.86%) |
| occurrences (all) | 14 | 3 | 69 |
| Constipation | | | |
| subjects affected / exposed | 23 / 93 (24.73%) | 0 / 18 (0.00%) | 158 / 632 (25.00%) |
| occurrences (all) | 27 | 0 | 235 |
| Dental cyst | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Diarrhoea | | | |

| | | | |
|-----------------------------|------------------|-----------------|--------------------|
| subjects affected / exposed | 52 / 93 (55.91%) | 4 / 18 (22.22%) | 282 / 632 (44.62%) |
| occurrences (all) | 104 | 5 | 539 |
| Haemorrhoids | | | |
| subjects affected / exposed | 7 / 93 (7.53%) | 1 / 18 (5.56%) | 22 / 632 (3.48%) |
| occurrences (all) | 7 | 1 | 24 |
| Dysphagia | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 0 / 18 (0.00%) | 17 / 632 (2.69%) |
| occurrences (all) | 8 | 0 | 24 |
| Gingival bleeding | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 9 / 632 (1.42%) |
| occurrences (all) | 3 | 0 | 9 |
| Dyspepsia | | | |
| subjects affected / exposed | 7 / 93 (7.53%) | 1 / 18 (5.56%) | 35 / 632 (5.54%) |
| occurrences (all) | 9 | 1 | 43 |
| Nausea | | | |
| subjects affected / exposed | 53 / 93 (56.99%) | 0 / 18 (0.00%) | 298 / 632 (47.15%) |
| occurrences (all) | 106 | 0 | 589 |
| Palatal ulcer | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 1 / 18 (5.56%) | 18 / 632 (2.85%) |
| occurrences (all) | 4 | 1 | 22 |
| Vomiting | | | |
| subjects affected / exposed | 29 / 93 (31.18%) | 1 / 18 (5.56%) | 152 / 632 (24.05%) |
| occurrences (all) | 46 | 1 | 243 |
| Stomatitis | | | |
| subjects affected / exposed | 24 / 93 (25.81%) | 3 / 18 (16.67%) | 144 / 632 (22.78%) |
| occurrences (all) | 36 | 3 | 225 |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 0 / 18 (0.00%) | 19 / 632 (3.01%) |
| occurrences (all) | 3 | 0 | 21 |
| Toothache | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 23 / 632 (3.64%) |
| occurrences (all) | 0 | 0 | 26 |
| Eructation | | | |

| | | | |
|--|------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences (all) | 0 | 0 | 2 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 0 / 18 (0.00%) | 25 / 632 (3.96%) |
| occurrences (all) | 4 | 0 | 27 |
| Odynophagia | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 5 / 632 (0.79%) |
| occurrences (all) | 2 | 0 | 5 |
| Cheilitis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 17 / 632 (2.69%) |
| occurrences (all) | 2 | 0 | 22 |
| Anal haemorrhage | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 9 / 632 (1.42%) |
| occurrences (all) | 3 | 0 | 11 |
| Hepatobiliary disorders | | | |
| Hepatomegaly | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences (all) | 1 | 0 | 3 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 9 / 93 (9.68%) | 2 / 18 (11.11%) | 63 / 632 (9.97%) |
| occurrences (all) | 10 | 2 | 64 |
| Dermatitis | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 1 / 18 (5.56%) | 4 / 632 (0.63%) |
| occurrences (all) | 2 | 1 | 5 |
| Nail ridging | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 1 / 18 (5.56%) | 3 / 632 (0.47%) |
| occurrences (all) | 2 | 1 | 3 |
| Erythema | | | |
| subjects affected / exposed | 11 / 93 (11.83%) | 1 / 18 (5.56%) | 21 / 632 (3.32%) |
| occurrences (all) | 19 | 4 | 22 |
| Eczema | | | |

| | | | |
|--|------------------|-----------------|-------------------|
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 4 / 632 (0.63%) |
| occurrences (all) | 2 | 0 | 4 |
| Dry skin | | | |
| subjects affected / exposed | 21 / 93 (22.58%) | 3 / 18 (16.67%) | 44 / 632 (6.96%) |
| occurrences (all) | 27 | 3 | 54 |
| Dermatitis contact | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 12 / 93 (12.90%) | 0 / 18 (0.00%) | 10 / 632 (1.58%) |
| occurrences (all) | 14 | 0 | 11 |
| Onychoclasia | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences (all) | 3 | 0 | 1 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 16 / 93 (17.20%) | 4 / 18 (22.22%) | 98 / 632 (15.51%) |
| occurrences (all) | 19 | 5 | 147 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 10 / 93 (10.75%) | 0 / 18 (0.00%) | 4 / 632 (0.63%) |
| occurrences (all) | 11 | 0 | 4 |
| Pruritus | | | |
| subjects affected / exposed | 10 / 93 (10.75%) | 2 / 18 (11.11%) | 34 / 632 (5.38%) |
| occurrences (all) | 10 | 2 | 42 |
| Rash | | | |
| subjects affected / exposed | 20 / 93 (21.51%) | 0 / 18 (0.00%) | 43 / 632 (6.80%) |
| occurrences (all) | 24 | 0 | 52 |
| Rash erythematous | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 0 / 18 (0.00%) | 6 / 632 (0.95%) |
| occurrences (all) | 4 | 0 | 6 |
| Rash macular | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Skin disorder | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences (all) | 2 | 0 | 1 |

| | | | |
|-----------------------------|----------------|----------------|-----------------|
| Skin fissures | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | 0 / 18 (0.00%) | 7 / 632 (1.11%) |
| occurrences (all) | 12 | 0 | 7 |
| Skin toxicity | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | 0 / 18 (0.00%) | 4 / 632 (0.63%) |
| occurrences (all) | 9 | 0 | 5 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermal cyst | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rosacea | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 8 / 632 (1.27%) |
| occurrences (all) | 2 | 0 | 12 |
| Erythema nodosum | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hair texture abnormal | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 6 / 632 (0.95%) |
| occurrences (all) | 1 | 0 | 6 |
| Hand dermatitis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 1 / 632 (0.16%) |
| occurrences (all) | 1 | 0 | 1 |
| Blister | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences (all) | 1 | 0 | 2 |
| Acne | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences (all) | 7 | 0 | 3 |

| | | | |
|---|------------------------|----------------------|--------------------------|
| Urticaria subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 2 | 0 / 18 (0.00%) 0 | 8 / 632 (1.27%) 14 |
| Renal and urinary disorders | | | |
| Dysuria subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | 1 / 18 (5.56%) 1 | 20 / 632 (3.16%) 21 |
| Proteinuria subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 2 | 0 / 18 (0.00%) 0 | 40 / 632 (6.33%) 56 |
| Renal colic subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 2 | 0 / 18 (0.00%) 0 | 0 / 632 (0.00%) 0 |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 0 / 632 (0.00%) 0 |
| Endocrine disorders | | | |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 18 / 632 (2.85%) 19 |
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 0 / 18 (0.00%) 0 | 26 / 632 (4.11%) 34 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 28 / 93 (30.11%) 48 | 3 / 18 (16.67%) 5 | 74 / 632 (11.71%) 100 |
| Back pain subjects affected / exposed occurrences (all) | 15 / 93 (16.13%) 17 | 2 / 18 (11.11%) 2 | 45 / 632 (7.12%) 59 |
| Bone pain subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 1 | 1 / 18 (5.56%) 1 | 10 / 632 (1.58%) 10 |
| Muscle spasms subjects affected / exposed occurrences (all) | 4 / 93 (4.30%) 4 | 0 / 18 (0.00%) 0 | 15 / 632 (2.37%) 15 |

| | | | |
|------------------------------------|------------------|----------------|------------------|
| Pain in extremity | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | 0 / 18 (0.00%) | 40 / 632 (6.33%) |
| occurrences (all) | 11 | 0 | 50 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 10 / 632 (1.58%) |
| occurrences (all) | 2 | 0 | 13 |
| Myalgia | | | |
| subjects affected / exposed | 13 / 93 (13.98%) | 1 / 18 (5.56%) | 28 / 632 (4.43%) |
| occurrences (all) | 18 | 1 | 34 |
| Muscle tightness | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 1 / 632 (0.16%) |
| occurrences (all) | 1 | 1 | 1 |
| Muscular weakness | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 7 / 632 (1.11%) |
| occurrences (all) | 2 | 0 | 7 |
| Osteoporosis | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences (all) | 2 | 0 | 2 |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 1 / 18 (5.56%) | 17 / 632 (2.69%) |
| occurrences (all) | 3 | 2 | 17 |
| Conjunctivitis | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 1 / 18 (5.56%) | 16 / 632 (2.53%) |
| occurrences (all) | 6 | 1 | 18 |
| Eye infection | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 1 / 18 (5.56%) | 7 / 632 (1.11%) |
| occurrences (all) | 3 | 1 | 7 |
| Nasopharyngitis | | | |

| | | | |
|-----------------------------------|----------------|-----------------|------------------|
| subjects affected / exposed | 4 / 93 (4.30%) | 1 / 18 (5.56%) | 42 / 632 (6.65%) |
| occurrences (all) | 4 | 1 | 56 |
| Onychomycosis | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 2 / 18 (11.11%) | 6 / 632 (0.95%) |
| occurrences (all) | 2 | 2 | 8 |
| Folliculitis | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | 0 / 18 (0.00%) | 4 / 632 (0.63%) |
| occurrences (all) | 11 | 0 | 5 |
| Paronychia | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | 0 / 18 (0.00%) | 4 / 632 (0.63%) |
| occurrences (all) | 22 | 0 | 4 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 23 / 632 (3.64%) |
| occurrences (all) | 1 | 0 | 23 |
| Tracheitis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 1 / 632 (0.16%) |
| occurrences (all) | 1 | 1 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | 1 / 18 (5.56%) | 42 / 632 (6.65%) |
| occurrences (all) | 6 | 1 | 52 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 2 / 18 (11.11%) | 27 / 632 (4.27%) |
| occurrences (all) | 6 | 2 | 40 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 6 / 632 (0.95%) |
| occurrences (all) | 2 | 0 | 6 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 8 / 632 (1.27%) |
| occurrences (all) | 1 | 0 | 8 |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 2 / 632 (0.32%) |
| occurrences (all) | 1 | 0 | 2 |
| Catheter site infection | | | |

| | | | |
|------------------------------------|------------------|----------------|--------------------|
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 3 / 632 (0.47%) |
| occurrences (all) | 1 | 0 | 3 |
| Device related infection | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 18 (0.00%) | 8 / 632 (1.27%) |
| occurrences (all) | 3 | 0 | 10 |
| Vulvitis | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 18 (0.00%) | 8 / 632 (1.27%) |
| occurrences (all) | 0 | 0 | 9 |
| Metabolism and nutrition disorders | | | |
| Food craving | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 0 / 632 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 20 / 93 (21.51%) | 0 / 18 (0.00%) | 130 / 632 (20.57%) |
| occurrences (all) | 26 | 0 | 171 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 18 (0.00%) | 29 / 632 (4.59%) |
| occurrences (all) | 1 | 0 | 43 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 18 (5.56%) | 17 / 632 (2.69%) |
| occurrences (all) | 1 | 1 | 23 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 1 / 18 (5.56%) | 18 / 632 (2.85%) |
| occurrences (all) | 5 | 1 | 37 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 7 / 93 (7.53%) | 0 / 18 (0.00%) | 9 / 632 (1.42%) |
| occurrences (all) | 9 | 0 | 9 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 0 / 18 (0.00%) | 10 / 632 (1.58%) |
| occurrences (all) | 3 | 0 | 10 |

| | | | |
|--|------------------------|---------------------|-------------------------|
| Hypokalaemia subjects affected / exposed occurrences (all) | 13 / 93 (13.98%) 20 | 1 / 18 (5.56%) 1 | 68 / 632 (10.76%) 91 |
| Dehydration subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 3 | 0 / 18 (0.00%) 0 | 11 / 632 (1.74%) 11 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 1 / 93 (1.08%) 2 | 0 / 18 (0.00%) 0 | 7 / 632 (1.11%) 9 |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 2 / 93 (2.15%) 2 | 0 / 18 (0.00%) 0 | 3 / 632 (0.47%) 3 |

| Non-serious adverse events | Cohort 2 (MP):5-FU/LV or capecitabine,bevacizumab,atezolizumab | Cohort 2 Control (MP): 5-FU/LV or capecitabin, bevacizumab | Early Progressing BRAFmut Cohort |
|---|--|--|----------------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 270 / 293 (92.15%) | 120 / 143 (83.92%) | 11 / 11 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Melanocytic naevus subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Cancer pain subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Tumour associated fever subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 49 / 293 (16.72%) 70 | 15 / 143 (10.49%) 19 | 1 / 11 (9.09%) 1 |
| Hypotension subjects affected / exposed occurrences (all) | 3 / 293 (1.02%) 3 | 1 / 143 (0.70%) 1 | 2 / 11 (18.18%) 2 |
| Phlebitis | | | |

| | | | |
|---|-------------------|-------------------|-----------------|
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Face oedema | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 40 / 293 (13.65%) | 12 / 143 (8.39%) | 1 / 11 (9.09%) |
| occurrences (all) | 58 | 20 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 52 / 293 (17.75%) | 23 / 143 (16.08%) | 3 / 11 (27.27%) |
| occurrences (all) | 77 | 27 | 3 |
| Influenza like illness | | | |
| subjects affected / exposed | 9 / 293 (3.07%) | 3 / 143 (2.10%) | 1 / 11 (9.09%) |
| occurrences (all) | 10 | 3 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 20 / 293 (6.83%) | 7 / 143 (4.90%) | 2 / 11 (18.18%) |
| occurrences (all) | 26 | 9 | 3 |
| Pain | | | |
| subjects affected / exposed | 4 / 293 (1.37%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 32 / 293 (10.92%) | 13 / 143 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 52 | 14 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 293 (2.73%) | 2 / 143 (1.40%) | 2 / 11 (18.18%) |
| occurrences (all) | 8 | 2 | 3 |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Malaise | | | |

| | | | |
|--|-------------------------|-------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 5 / 293 (1.71%) 5 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 2 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 2 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Cough subjects affected / exposed occurrences (all) | 30 / 293 (10.24%) 39 | 9 / 143 (6.29%) 11 | 0 / 11 (0.00%) 0 |
| Dysphonia subjects affected / exposed occurrences (all) | 15 / 293 (5.12%) 18 | 3 / 143 (2.10%) 3 | 0 / 11 (0.00%) 0 |
| Dyspnoea subjects affected / exposed occurrences (all) | 12 / 293 (4.10%) 12 | 3 / 143 (2.10%) 3 | 2 / 11 (18.18%) 3 |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 3 / 293 (1.02%) 3 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Nasal ulcer subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Nasal dryness subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 2 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Epistaxis subjects affected / exposed occurrences (all) | 23 / 293 (7.85%) 29 | 16 / 143 (11.19%) 20 | 3 / 11 (27.27%) 3 |
| Hiccups subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Oropharyngeal pain | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 6 / 293 (2.05%) 9 | 3 / 143 (2.10%) 4 | 0 / 11 (0.00%) 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 4 / 293 (1.37%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 10 / 293 (3.41%) | 3 / 143 (2.10%) | 2 / 11 (18.18%) |
| occurrences (all) | 10 | 3 | 2 |
| Depression | | | |
| subjects affected / exposed | 3 / 293 (1.02%) | 5 / 143 (3.50%) | 2 / 11 (18.18%) |
| occurrences (all) | 3 | 5 | 2 |
| Product issues | | | |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 8 / 293 (2.73%) | 6 / 143 (4.20%) | 0 / 11 (0.00%) |
| occurrences (all) | 14 | 9 | 0 |
| Amylase increased | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 10 / 293 (3.41%) | 6 / 143 (4.20%) | 0 / 11 (0.00%) |
| occurrences (all) | 13 | 7 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 5 / 293 (1.71%) | 4 / 143 (2.80%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 5 | 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |

| | | | |
|----------------------------------|------------------|-----------------|----------------|
| subjects affected / exposed | 4 / 293 (1.37%) | 1 / 143 (0.70%) | 1 / 11 (9.09%) |
| occurrences (all) | 4 | 4 | 1 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 8 / 293 (2.73%) | 5 / 143 (3.50%) | 0 / 11 (0.00%) |
| occurrences (all) | 10 | 6 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 3 | 0 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 7 / 293 (2.39%) | 3 / 143 (2.10%) | 1 / 11 (9.09%) |
| occurrences (all) | 11 | 4 | 1 |
| Platelet count decreased | | | |
| subjects affected / exposed | 6 / 293 (2.05%) | 3 / 143 (2.10%) | 0 / 11 (0.00%) |
| occurrences (all) | 19 | 4 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 11 / 293 (3.75%) | 2 / 143 (1.40%) | 0 / 11 (0.00%) |
| occurrences (all) | 12 | 3 | 0 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 3 / 293 (1.02%) | 1 / 143 (0.70%) | 1 / 11 (9.09%) |
| occurrences (all) | 3 | 1 | 1 |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Blood lactate dehydrogenase | | | |

| | | | |
|---|------------------------|-----------------------|----------------------|
| increased subjects affected / exposed occurrences (all) | 3 / 293 (1.02%) 3 | 2 / 143 (1.40%) 2 | 0 / 11 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction subjects affected / exposed occurrences (all) | 10 / 293 (3.41%) 12 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Lumbar vertebral fracture subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 1 / 143 (0.70%) 1 | 1 / 11 (9.09%) 1 |
| Sunburn subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 1 / 143 (0.70%) 1 | 3 / 11 (27.27%) 3 |
| Gastrointestinal stoma complication subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Stoma site pain subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 2 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Wound dehiscence subjects affected / exposed occurrences (all) | 3 / 293 (1.02%) 3 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 6 / 293 (2.05%) 7 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 8 / 293 (2.73%) 8 | 3 / 143 (2.10%) 3 | 1 / 11 (9.09%) 1 |
| Headache subjects affected / exposed occurrences (all) | 24 / 293 (8.19%) 83 | 5 / 143 (3.50%) 15 | 0 / 11 (0.00%) 0 |
| Peripheral motor neuropathy subjects affected / exposed occurrences (all) | 3 / 293 (1.02%) 3 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Neurotoxicity | | | |

| | | | |
|---|-------------------|-------------------|----------------|
| subjects affected / exposed | 2 / 293 (0.68%) | 2 / 143 (1.40%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 18 / 293 (6.14%) | 10 / 143 (6.99%) | 0 / 11 (0.00%) |
| occurrences (all) | 21 | 11 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 18 / 293 (6.14%) | 9 / 143 (6.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 21 | 9 | 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 32 / 293 (10.92%) | 15 / 143 (10.49%) | 0 / 11 (0.00%) |
| occurrences (all) | 38 | 16 | 0 |
| Polyneuropathy | | | |
| subjects affected / exposed | 6 / 293 (2.05%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences (all) | 6 | 2 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Somnolence | | | |
| subjects affected / exposed | 4 / 293 (1.37%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Taste disorder | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 1 | 1 |
| Sensory loss | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ageusia | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 21 / 293 (7.17%) | 8 / 143 (5.59%) | 1 / 11 (9.09%) |
| occurrences (all) | 27 | 13 | 1 |
| Leukopenia | | | |
| subjects affected / exposed | 4 / 293 (1.37%) | 3 / 143 (2.10%) | 0 / 11 (0.00%) |
| occurrences (all) | 8 | 3 | 0 |

| | | | |
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| Neutropenia subjects affected / exposed occurrences (all) | 12 / 293 (4.10%) 12 | 8 / 143 (5.59%) 17 | 0 / 11 (0.00%) 0 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 10 / 293 (3.41%) 12 | 4 / 143 (2.80%) 10 | 0 / 11 (0.00%) 0 |
| Ear and labyrinth disorders Auditory meatus external erosion subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 3 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Lacrimation increased subjects affected / exposed occurrences (all) | 4 / 293 (1.37%) 5 | 5 / 143 (3.50%) 5 | 0 / 11 (0.00%) 0 |
| Periorbital oedema subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 2 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Dry eye subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 2 / 143 (1.40%) 2 | 1 / 11 (9.09%) 1 |
| Visual impairment subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 2 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Gastrointestinal disorders Angular cheilitis subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 39 / 293 (13.31%) 44 | 12 / 143 (8.39%) 15 | 4 / 11 (36.36%) 5 |
| Abdominal pain upper | | | |

| | | | |
|-----------------------------|-------------------|-------------------|-----------------|
| subjects affected / exposed | 18 / 293 (6.14%) | 11 / 143 (7.69%) | 0 / 11 (0.00%) |
| occurrences (all) | 22 | 15 | 0 |
| Constipation | | | |
| subjects affected / exposed | 38 / 293 (12.97%) | 17 / 143 (11.89%) | 1 / 11 (9.09%) |
| occurrences (all) | 48 | 26 | 1 |
| Dental cyst | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 78 / 293 (26.62%) | 21 / 143 (14.69%) | 5 / 11 (45.45%) |
| occurrences (all) | 120 | 36 | 5 |
| Haemorrhoids | | | |
| subjects affected / exposed | 5 / 293 (1.71%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 5 / 293 (1.71%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 10 / 293 (3.41%) | 4 / 143 (2.80%) | 0 / 11 (0.00%) |
| occurrences (all) | 12 | 4 | 0 |
| Nausea | | | |
| subjects affected / exposed | 64 / 293 (21.84%) | 27 / 143 (18.88%) | 3 / 11 (27.27%) |
| occurrences (all) | 134 | 41 | 4 |
| Palatal ulcer | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 6 / 293 (2.05%) | 4 / 143 (2.80%) | 1 / 11 (9.09%) |
| occurrences (all) | 6 | 6 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 39 / 293 (13.31%) | 8 / 143 (5.59%) | 4 / 11 (36.36%) |
| occurrences (all) | 61 | 11 | 5 |
| Stomatitis | | | |

| | | | |
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| subjects affected / exposed occurrences (all) | 35 / 293 (11.95%) 50 | 11 / 143 (7.69%) 19 | 1 / 11 (9.09%) 2 |
| Dry mouth subjects affected / exposed occurrences (all) | 4 / 293 (1.37%) 4 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Toothache subjects affected / exposed occurrences (all) | 8 / 293 (2.73%) 8 | 2 / 143 (1.40%) 2 | 0 / 11 (0.00%) 0 |
| Eructation subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 6 / 293 (2.05%) 8 | 1 / 143 (0.70%) 1 | 2 / 11 (18.18%) 2 |
| Odynophagia subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Cheilitis subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Flatulence subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 2 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Anal haemorrhage subjects affected / exposed occurrences (all) | 4 / 293 (1.37%) 5 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Hepatobiliary disorders Hepatomegaly subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 8 / 293 (2.73%) 8 | 2 / 143 (1.40%) 2 | 0 / 11 (0.00%) 0 |
| Dermatitis | | | |

| | | | |
|--|-------------------|-------------------|-----------------|
| subjects affected / exposed | 3 / 293 (1.02%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Nail ridging | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 3 / 143 (2.10%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 3 | 1 |
| Erythema | | | |
| subjects affected / exposed | 11 / 293 (3.75%) | 2 / 143 (1.40%) | 2 / 11 (18.18%) |
| occurrences (all) | 12 | 2 | 4 |
| Eczema | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 18 / 293 (6.14%) | 3 / 143 (2.10%) | 3 / 11 (27.27%) |
| occurrences (all) | 21 | 6 | 3 |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 4 / 293 (1.37%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 4 | 0 | 1 |
| Onychoclasis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 44 / 293 (15.02%) | 25 / 143 (17.48%) | 2 / 11 (18.18%) |
| occurrences (all) | 66 | 40 | 2 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 20 / 293 (6.83%) | 6 / 143 (4.20%) | 3 / 11 (27.27%) |
| occurrences (all) | 25 | 6 | 3 |
| Rash | | | |
| subjects affected / exposed | 24 / 293 (8.19%) | 1 / 143 (0.70%) | 4 / 11 (36.36%) |
| occurrences (all) | 30 | 1 | 4 |

| | | | |
|-----------------------------|-----------------|-----------------|----------------|
| Rash erythematous | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin fissures | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 1 |
| Skin toxicity | | | |
| subjects affected / exposed | 4 / 293 (1.37%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 5 | 0 | 1 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Dermal cyst | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Rosacea | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 4 / 293 (1.37%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 6 | 0 | 1 |
| Erythema nodosum | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Hair texture abnormal | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin exfoliation | | | |
| subjects affected / exposed | 5 / 293 (1.71%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |

| | | | |
|---|-------------------------|-----------------------|----------------------|
| Hand dermatitis subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Blister subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Acne subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 1 / 143 (0.70%) 1 | 3 / 11 (27.27%) 4 |
| Urticaria subjects affected / exposed occurrences (all) | 4 / 293 (1.37%) 5 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Renal and urinary disorders | | | |
| Dysuria subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 2 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Proteinuria subjects affected / exposed occurrences (all) | 17 / 293 (5.80%) 25 | 4 / 143 (2.80%) 4 | 0 / 11 (0.00%) 0 |
| Renal colic subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Endocrine disorders | | | |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 16 / 293 (5.46%) 17 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Hypothyroidism subjects affected / exposed occurrences (all) | 24 / 293 (8.19%) 32 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 50 / 293 (17.06%) 67 | 8 / 143 (5.59%) 10 | 5 / 11 (45.45%) 5 |

| | | | |
|-----------------------------|------------------|-----------------|-----------------|
| Back pain | | | |
| subjects affected / exposed | 22 / 293 (7.51%) | 9 / 143 (6.29%) | 3 / 11 (27.27%) |
| occurrences (all) | 32 | 9 | 4 |
| Bone pain | | | |
| subjects affected / exposed | 6 / 293 (2.05%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 5 / 293 (1.71%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 13 / 293 (4.44%) | 8 / 143 (5.59%) | 0 / 11 (0.00%) |
| occurrences (all) | 18 | 9 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 5 / 293 (1.71%) | 2 / 143 (1.40%) | 0 / 11 (0.00%) |
| occurrences (all) | 6 | 2 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 15 / 293 (5.12%) | 3 / 143 (2.10%) | 1 / 11 (9.09%) |
| occurrences (all) | 17 | 3 | 1 |
| Muscle tightness | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 2 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 2 / 143 (1.40%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 2 | 1 |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 5 / 293 (1.71%) | 3 / 143 (2.10%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 3 | 0 |
| Conjunctivitis | | | |

| | | | |
|-----------------------------------|------------------|------------------|-----------------|
| subjects affected / exposed | 5 / 293 (1.71%) | 2 / 143 (1.40%) | 0 / 11 (0.00%) |
| occurrences (all) | 6 | 2 | 0 |
| Eye infection | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 0 / 143 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 15 / 293 (5.12%) | 10 / 143 (6.99%) | 1 / 11 (9.09%) |
| occurrences (all) | 21 | 12 | 1 |
| Onychomycosis | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 2 / 143 (1.40%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 1 / 143 (0.70%) | 2 / 11 (18.18%) |
| occurrences (all) | 3 | 1 | 3 |
| Paronychia | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 1 / 143 (0.70%) | 2 / 11 (18.18%) |
| occurrences (all) | 2 | 1 | 8 |
| Rhinitis | | | |
| subjects affected / exposed | 5 / 293 (1.71%) | 3 / 143 (2.10%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 3 | 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 293 (0.00%) | 1 / 143 (0.70%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 293 (4.10%) | 4 / 143 (2.80%) | 1 / 11 (9.09%) |
| occurrences (all) | 13 | 4 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 12 / 293 (4.10%) | 2 / 143 (1.40%) | 0 / 11 (0.00%) |
| occurrences (all) | 22 | 2 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 1 | 1 |
| Staphylococcal infection | | | |

| | | | |
|---|------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Vascular device infection subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 1 / 143 (0.70%) 1 | 1 / 11 (9.09%) 1 |
| Febrile infection subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Catheter site infection subjects affected / exposed occurrences (all) | 1 / 293 (0.34%) 1 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Device related infection subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 3 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Vulvitis subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Anal abscess subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Cystitis subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 2 | 1 / 143 (0.70%) 1 | 0 / 11 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Food craving subjects affected / exposed occurrences (all) | 0 / 293 (0.00%) 0 | 0 / 143 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Decreased appetite subjects affected / exposed occurrences (all) | 24 / 293 (8.19%) 26 | 14 / 143 (9.79%) 15 | 2 / 11 (18.18%) 2 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 5 / 293 (1.71%) 6 | 2 / 143 (1.40%) 5 | 0 / 11 (0.00%) 0 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 2 / 293 (0.68%) 2 | 2 / 143 (1.40%) 4 | 0 / 11 (0.00%) 0 |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| Hypocalcaemia | | | |
| subjects affected / exposed | 5 / 293 (1.71%) | 6 / 143 (4.20%) | 0 / 11 (0.00%) |
| occurrences (all) | 10 | 10 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 4 / 293 (1.37%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 4 | 0 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 293 (0.68%) | 3 / 143 (2.10%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 6 / 293 (2.05%) | 8 / 143 (5.59%) | 2 / 11 (18.18%) |
| occurrences (all) | 7 | 9 | 2 |
| Dehydration | | | |
| subjects affected / exposed | 4 / 293 (1.37%) | 0 / 143 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 4 | 0 | 2 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 4 / 293 (1.37%) | 1 / 143 (0.70%) | 1 / 11 (9.09%) |
| occurrences (all) | 5 | 2 | 2 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 293 (0.34%) | 1 / 143 (0.70%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 1 | 1 |

| Non-serious adverse events | Cohort 3 (MP): capecitabine, trastuzumab, pertuzumab | Cohort 3 Control (MP): 5-FU/LV or capecitabine, bevacizumab | Cohort 4 (IP) |
|---|---|---|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 2 / 2 (100.00%) | 298 / 309 (96.44%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------|---------------|-------------------|
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 62 / 309 (20.06%) |
| occurrences (all) | 0 | 0 | 79 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 8 / 309 (2.59%) |
| occurrences (all) | 0 | 0 | 8 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences (all) | 0 | 0 | 2 |
| General disorders and administration site conditions | | | |
| Face oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 5 / 309 (1.62%) |
| occurrences (all) | 0 | 0 | 5 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 63 / 309 (20.39%) |
| occurrences (all) | 0 | 0 | 111 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 87 / 309 (28.16%) |
| occurrences (all) | 1 | 0 | 138 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 10 / 309 (3.24%) |
| occurrences (all) | 0 | 0 | 10 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 57 / 309 (18.45%) |
| occurrences (all) | 1 | 0 | 72 |
| Pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 1 | 0 | 3 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 56 / 309 (18.12%) |
| occurrences (all) | 0 | 0 | 76 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 16 / 309 (5.18%) |
| occurrences (all) | 0 | 0 | 18 |
| Catheter site pain | | | |

| | | | |
|---|---------------------|--------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 2 / 309 (0.65%) 2 |
| General physical health deterioration subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 1 / 309 (0.32%) 1 |
| Malaise subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 4 / 309 (1.29%) 4 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 4 / 309 (1.29%) 5 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Cough subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 27 / 309 (8.74%) 31 |
| Dysphonia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 14 / 309 (4.53%) 14 |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 20 / 309 (6.47%) 21 |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 5 / 309 (1.62%) 5 |
| Nasal ulcer subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Nasal dryness subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 1 / 309 (0.32%) 1 |
| Epistaxis | | | |

| | | | |
|--|---------------------|----------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 2 (100.00%) 2 | 61 / 309 (19.74%) 70 |
| Hiccups subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 8 / 309 (2.59%) 9 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 5 / 309 (1.62%) 5 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 9 / 309 (2.91%) 9 |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 12 / 309 (3.88%) 13 |
| Depression subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 2 / 309 (0.65%) 2 |
| Product issues Device occlusion subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 3 / 309 (0.97%) 3 |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 17 / 309 (5.50%) 20 |
| Amylase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 8 / 309 (2.59%) 8 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 20 / 309 (6.47%) 22 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 12 / 309 (3.88%) 16 |
| Ejection fraction decreased | | | |

| | | | |
|--|----------------|---------------|-------------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 6 / 309 (1.94%) |
| occurrences (all) | 0 | 0 | 7 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 32 / 309 (10.36%) |
| occurrences (all) | 1 | 0 | 40 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 7 / 309 (2.27%) |
| occurrences (all) | 0 | 0 | 7 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 4 / 309 (1.29%) |
| occurrences (all) | 0 | 0 | 4 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 9 / 309 (2.91%) |
| occurrences (all) | 0 | 0 | 12 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 28 / 309 (9.06%) |
| occurrences (all) | 0 | 0 | 42 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 27 / 309 (8.74%) |
| occurrences (all) | 0 | 0 | 37 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 8 / 309 (2.59%) |
| occurrences (all) | 0 | 0 | 14 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 30 / 309 (9.71%) |
| occurrences (all) | 0 | 0 | 31 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---------------------|--------------------|------------------------|
| Body temperature increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 6 / 309 (1.94%) 8 |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 4 / 309 (1.29%) 4 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 11 / 309 (3.56%) 17 |
| Lumbar vertebral fracture subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Sunburn subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Gastrointestinal stoma complication subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Stoma site pain subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Wound dehiscence subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 1 / 309 (0.32%) 1 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 12 / 309 (3.88%) 12 |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 21 / 309 (6.80%) 26 |
| Headache | | | |

| | | | |
|--------------------------------------|---------------|---------------|-------------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 28 / 309 (9.06%) |
| occurrences (all) | 0 | 0 | 50 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 11 / 309 (3.56%) |
| occurrences (all) | 0 | 0 | 12 |
| Neurotoxicity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 27 / 309 (8.74%) |
| occurrences (all) | 0 | 0 | 46 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 43 / 309 (13.92%) |
| occurrences (all) | 0 | 0 | 57 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 57 / 309 (18.45%) |
| occurrences (all) | 0 | 0 | 84 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 58 / 309 (18.77%) |
| occurrences (all) | 0 | 0 | 91 |
| Polyneuropathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 9 / 309 (2.91%) |
| occurrences (all) | 0 | 0 | 12 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 2 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Taste disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Sensory loss | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ageusia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences (all) | 0 | 0 | 4 |
| Blood and lymphatic system disorders | | | |

| | | | |
|----------------------------------|----------------|---------------|-------------------|
| Anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 49 / 309 (15.86%) |
| occurrences (all) | 0 | 0 | 62 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 11 / 309 (3.56%) |
| occurrences (all) | 0 | 0 | 14 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 78 / 309 (25.24%) |
| occurrences (all) | 0 | 0 | 123 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 22 / 309 (7.12%) |
| occurrences (all) | 0 | 0 | 45 |
| Ear and labyrinth disorders | | | |
| Auditory meatus external erosion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 4 / 309 (1.29%) |
| occurrences (all) | 0 | 0 | 4 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lacrimation increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastrointestinal disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|--------------------|
| Angular cheilitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 45 / 309 (14.56%) |
| occurrences (all) | 0 | 0 | 56 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 20 / 309 (6.47%) |
| occurrences (all) | 0 | 0 | 21 |
| Constipation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 2 (50.00%) | 58 / 309 (18.77%) |
| occurrences (all) | 0 | 1 | 74 |
| Dental cyst | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 2 (0.00%) | 134 / 309 (43.37%) |
| occurrences (all) | 5 | 0 | 276 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 7 / 309 (2.27%) |
| occurrences (all) | 0 | 0 | 7 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 10 / 309 (3.24%) |
| occurrences (all) | 0 | 0 | 10 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 2 (50.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 19 / 309 (6.15%) |
| occurrences (all) | 0 | 0 | 19 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 129 / 309 (41.75%) |
| occurrences (all) | 0 | 0 | 246 |
| Palatal ulcer | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|----------------------------------|----------------|---------------|-------------------|
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences (all) | 0 | 0 | 4 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 66 / 309 (21.36%) |
| occurrences (all) | 0 | 0 | 101 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 40 / 309 (12.94%) |
| occurrences (all) | 0 | 0 | 52 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 9 / 309 (2.91%) |
| occurrences (all) | 0 | 0 | 9 |
| Toothache | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences (all) | 1 | 0 | 3 |
| Eructation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences (all) | 0 | 0 | 4 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 6 / 309 (1.94%) |
| occurrences (all) | 0 | 0 | 6 |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Hepatobiliary disorders | | | |
| Hepatomegaly | | | |

| | | | |
|---|----------------------|--------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 19 / 309 (6.15%) 19 |
| Dermatitis | | | |
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 1 / 309 (0.32%) 2 |
| Nail ridging | | | |
| subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Erythema | | | |
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 4 / 309 (1.29%) 4 |
| Eczema | | | |
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Dry skin | | | |
| subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 20 / 309 (6.47%) 20 |
| Dermatitis contact | | | |
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 20 / 309 (6.47%) 23 |
| Onychoclasis | | | |
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 309 (0.00%) 0 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed occurrences (all) | 3 / 3 (100.00%) 6 | 0 / 2 (0.00%) 0 | 19 / 309 (6.15%) 19 |
| Photosensitivity reaction | | | |

| | | | |
|-----------------------------|---------------|---------------|-------------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 16 / 309 (5.18%) |
| occurrences (all) | 0 | 0 | 26 |
| Rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 38 / 309 (12.30%) |
| occurrences (all) | 0 | 0 | 46 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences (all) | 0 | 0 | 3 |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermal cyst | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rosacea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 5 / 309 (1.62%) |
| occurrences (all) | 0 | 0 | 6 |
| Erythema nodosum | | | |

| | | | |
|-----------------------------|---------------|----------------|------------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hair texture abnormal | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 2 (50.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hand dermatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blister | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Acne | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 4 / 309 (1.29%) |
| occurrences (all) | 0 | 0 | 6 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 10 / 309 (3.24%) |
| occurrences (all) | 0 | 0 | 12 |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 7 / 309 (2.27%) |
| occurrences (all) | 0 | 0 | 12 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |

| | | | |
|---|----------------|---------------|------------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences (all) | 0 | 0 | 3 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 19 / 309 (6.15%) |
| occurrences (all) | 0 | 0 | 22 |
| Back pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 16 / 309 (5.18%) |
| occurrences (all) | 0 | 0 | 17 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences (all) | 0 | 0 | 4 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 4 / 309 (1.29%) |
| occurrences (all) | 1 | 0 | 4 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 12 / 309 (3.88%) |
| occurrences (all) | 0 | 0 | 14 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 18 / 309 (5.83%) |
| occurrences (all) | 0 | 0 | 23 |
| Muscle tightness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 4 / 309 (1.29%) |
| occurrences (all) | 0 | 0 | 4 |
| Osteoporosis | | | |

| | | | |
|------------------------------------|----------------|---------------|------------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences (all) | 0 | 0 | 3 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 5 / 309 (1.62%) |
| occurrences (all) | 0 | 0 | 5 |
| Eye infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences (all) | 0 | 0 | 2 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 15 / 309 (4.85%) |
| occurrences (all) | 1 | 0 | 17 |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 6 / 309 (1.94%) |
| occurrences (all) | 0 | 0 | 7 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|------------------------------------|----------------|---------------|------------------|
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 18 / 309 (5.83%) |
| occurrences (all) | 0 | 0 | 25 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 12 / 309 (3.88%) |
| occurrences (all) | 0 | 0 | 13 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 5 / 309 (1.62%) |
| occurrences (all) | 0 | 0 | 5 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Febrile infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 1 / 309 (0.32%) |
| occurrences (all) | 0 | 0 | 1 |
| Vulvitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 2 / 309 (0.65%) |
| occurrences (all) | 1 | 0 | 2 |
| Metabolism and nutrition disorders | | | |
| Food craving | | | |

| | | | |
|-----------------------------|----------------|---------------|-------------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 47 / 309 (15.21%) |
| occurrences (all) | 0 | 0 | 55 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 16 / 309 (5.18%) |
| occurrences (all) | 0 | 0 | 20 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 6 / 309 (1.94%) |
| occurrences (all) | 0 | 0 | 8 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 7 / 309 (2.27%) |
| occurrences (all) | 0 | 0 | 10 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 6 / 309 (1.94%) |
| occurrences (all) | 0 | 0 | 7 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 6 / 309 (1.94%) |
| occurrences (all) | 0 | 0 | 8 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 2 (0.00%) | 16 / 309 (5.18%) |
| occurrences (all) | 1 | 0 | 18 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences (all) | 0 | 0 | 4 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 3 / 309 (0.97%) |
| occurrences (all) | 0 | 0 | 3 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 2 (0.00%) | 0 / 309 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------------|--|---|--|
| Non-serious adverse events | Cohort 4 (MP): Cobimetinib,atezoliz umab | Cohort 4 Control (MP): 5-FU/LV or capecitabin, bevacizumab | Cohort 1 (Maintenance Phase[MP]):5- FU/LV,cetuximab,ve murafenib |
|-----------------------------------|--|---|--|

| | | | |
|---|------------------------|----------------------|-----------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 61 / 64 (95.31%) | 29 / 34 (85.29%) | 40 / 40 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Melanocytic naevus subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Cancer pain subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 1 / 34 (2.94%) 1 | 0 / 40 (0.00%) 0 |
| Tumour associated fever subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 4 | 5 / 34 (14.71%) 7 | 1 / 40 (2.50%) 1 |
| Hypotension subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 0 / 34 (0.00%) 0 | 4 / 40 (10.00%) 4 |
| Phlebitis subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 2 |
| General disorders and administration site conditions Face oedema subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 5 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Asthenia subjects affected / exposed occurrences (all) | 13 / 64 (20.31%) 18 | 3 / 34 (8.82%) 3 | 5 / 40 (12.50%) 9 |
| Fatigue subjects affected / exposed occurrences (all) | 12 / 64 (18.75%) 20 | 7 / 34 (20.59%) 8 | 9 / 40 (22.50%) 11 |
| Influenza like illness subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 1 / 34 (2.94%) 1 | 2 / 40 (5.00%) 2 |
| Mucosal inflammation | | | |

| | | | |
|--|------------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 5 | 1 / 34 (2.94%) 1 | 7 / 40 (17.50%) 8 |
| Pain subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 3 / 40 (7.50%) 3 |
| Pyrexia subjects affected / exposed occurrences (all) | 20 / 64 (31.25%) 27 | 3 / 34 (8.82%) 3 | 8 / 40 (20.00%) 8 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 6 / 64 (9.38%) 8 | 1 / 34 (2.94%) 1 | 3 / 40 (7.50%) 6 |
| Catheter site pain subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| General physical health deterioration subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Malaise subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 | 3 / 40 (7.50%) 3 |
| Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Cough subjects affected / exposed occurrences (all) | 7 / 64 (10.94%) 7 | 3 / 34 (8.82%) 3 | 5 / 40 (12.50%) 6 |
| Dysphonia subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Dyspnoea | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 2 | 1 / 34 (2.94%) 1 | 2 / 40 (5.00%) 2 |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 1 / 34 (2.94%) 1 | 1 / 40 (2.50%) 2 |
| Nasal ulcer subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Nasal dryness subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 1 / 34 (2.94%) 1 | 0 / 40 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 6 / 64 (9.38%) 6 | 3 / 34 (8.82%) 4 | 4 / 40 (10.00%) 4 |
| Hiccups subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Insomnia subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 0 / 34 (0.00%) 0 | 2 / 40 (5.00%) 2 |
| Depression subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Product issues Device occlusion subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Investigations | | | |

| | | | |
|--|------------------------|---------------------|----------------------|
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 12 / 64 (18.75%) 13 | 0 / 34 (0.00%) 0 | 2 / 40 (5.00%) 2 |
| Amylase increased subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 4 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 15 / 64 (23.44%) 15 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 6 / 64 (9.38%) 6 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Ejection fraction decreased subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 6 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 31 / 64 (48.44%) 39 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 | 4 / 40 (10.00%) 6 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 | 2 / 40 (5.00%) 3 |
| Lipase increased subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 7 | 0 / 34 (0.00%) 0 | 3 / 40 (7.50%) 3 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 2 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 6 / 64 (9.38%) 7 | 1 / 34 (2.94%) 1 | 1 / 40 (2.50%) 1 |
| Weight increased | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed | 3 / 64 (4.69%) | 2 / 34 (5.88%) | 1 / 40 (2.50%) |
| occurrences (all) | 7 | 2 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 6 / 64 (9.38%) | 0 / 34 (0.00%) | 4 / 40 (10.00%) |
| occurrences (all) | 6 | 0 | 4 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 2 | 0 | 3 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sunburn | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal stoma complication | | | |

| | | | |
|---|---------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Stoma site pain subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Wound dehiscence subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 4 | 1 / 34 (2.94%) 1 | 4 / 40 (10.00%) 4 |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 4 / 40 (10.00%) 4 |
| Headache subjects affected / exposed occurrences (all) | 6 / 64 (9.38%) 8 | 3 / 34 (8.82%) 5 | 2 / 40 (5.00%) 2 |
| Peripheral motor neuropathy subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 | 2 / 40 (5.00%) 3 |
| Neurotoxicity subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 1 / 34 (2.94%) 1 | 3 / 40 (7.50%) 3 |
| Paraesthesia subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 1 / 34 (2.94%) 1 | 4 / 40 (10.00%) 4 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 2 | 5 / 34 (14.71%) 5 | 1 / 40 (2.50%) 1 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 6 | 4 / 34 (11.76%) 4 | 4 / 40 (10.00%) 5 |
| Polyneuropathy subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |

| | | | |
|--|-----------------------|---------------------|-----------------------|
| Restless legs syndrome subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Somnolence subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 2 / 40 (5.00%) 2 |
| Taste disorder subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Sensory loss subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Ageusia subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 1 / 34 (2.94%) 1 | 0 / 40 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 8 / 64 (12.50%) 10 | 1 / 34 (2.94%) 1 | 7 / 40 (17.50%) 10 |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 1 / 34 (2.94%) 1 | 1 / 40 (2.50%) 1 |
| Neutropenia subjects affected / exposed occurrences (all) | 7 / 64 (10.94%) 9 | 3 / 34 (8.82%) 4 | 2 / 40 (5.00%) 2 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 4 | 1 / 34 (2.94%) 5 | 0 / 40 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Auditory meatus external erosion subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Eye disorders | | | |
| Cataract subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 0 / 34 (0.00%) 0 | 4 / 40 (10.00%) 5 |
| Conjunctival haemorrhage | | | |

| | | | |
|-----------------------------------|------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lacrimation increased | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 34 (2.94%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Angular cheilitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 12 / 64 (18.75%) | 5 / 34 (14.71%) | 8 / 40 (20.00%) |
| occurrences (all) | 15 | 5 | 10 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 64 (7.81%) | 1 / 34 (2.94%) | 2 / 40 (5.00%) |
| occurrences (all) | 6 | 1 | 2 |
| Constipation | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | 2 / 34 (5.88%) | 5 / 40 (12.50%) |
| occurrences (all) | 9 | 2 | 6 |
| Dental cyst | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 40 / 64 (62.50%) | 8 / 34 (23.53%) | 16 / 40 (40.00%) |
| occurrences (all) | 87 | 11 | 43 |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 2 | 0 | 1 |

| | | | |
|----------------------------------|------------------|-----------------|------------------|
| Dysphagia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 2 / 34 (5.88%) | 2 / 40 (5.00%) |
| occurrences (all) | 1 | 2 | 4 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 17 / 64 (26.56%) | 6 / 34 (17.65%) | 16 / 40 (40.00%) |
| occurrences (all) | 22 | 22 | 23 |
| Palatal ulcer | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 13 / 64 (20.31%) | 3 / 34 (8.82%) | 8 / 40 (20.00%) |
| occurrences (all) | 19 | 9 | 12 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 3 / 34 (8.82%) | 5 / 40 (12.50%) |
| occurrences (all) | 1 | 3 | 6 |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 3 | 0 | 1 |
| Toothache | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eructation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------|----------------|------------------|
| Odynophagia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 34 (2.94%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Anal haemorrhage | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hepatomegaly | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 34 (2.94%) | 1 / 40 (2.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nail ridging | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 8 / 40 (20.00%) |
| occurrences (all) | 1 | 0 | 11 |
| Eczema | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Dry skin | | | |
| subjects affected / exposed | 6 / 64 (9.38%) | 1 / 34 (2.94%) | 12 / 40 (30.00%) |
| occurrences (all) | 6 | 1 | 16 |
| Dermatitis contact | | | |

| | | | |
|--|------------------|----------------|------------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 18 / 64 (28.13%) | 2 / 34 (5.88%) | 11 / 40 (27.50%) |
| occurrences (all) | 20 | 2 | 13 |
| Onychoclasia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 3 / 40 (7.50%) |
| occurrences (all) | 0 | 0 | 3 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 3 / 34 (8.82%) | 5 / 40 (12.50%) |
| occurrences (all) | 1 | 3 | 5 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 9 / 40 (22.50%) |
| occurrences (all) | 0 | 0 | 10 |
| Pruritus | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | 1 / 34 (2.94%) | 5 / 40 (12.50%) |
| occurrences (all) | 14 | 1 | 5 |
| Rash | | | |
| subjects affected / exposed | 28 / 64 (43.75%) | 0 / 34 (0.00%) | 13 / 40 (32.50%) |
| occurrences (all) | 33 | 0 | 17 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 3 / 40 (7.50%) |
| occurrences (all) | 0 | 0 | 4 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 1 / 34 (2.94%) | 7 / 40 (17.50%) |
| occurrences (all) | 1 | 1 | 11 |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 4 / 40 (10.00%) |
| occurrences (all) | 0 | 0 | 7 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermal cyst | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rosacea | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 3 | 0 | 1 |
| Erythema nodosum | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hair texture abnormal | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Hand dermatitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blister | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Acne | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 0 | 0 | 2 |
| Urticaria | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |

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|---|----------------------|---------------------|------------------------|
| subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 2 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Proteinuria subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 2 / 34 (5.88%) 4 | 1 / 40 (2.50%) 1 |
| Renal colic subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Hypothyroidism subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 8 / 64 (12.50%) 8 | 3 / 34 (8.82%) 5 | 18 / 40 (45.00%) 30 |
| Back pain subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 5 | 3 / 34 (8.82%) 3 | 5 / 40 (12.50%) 5 |
| Bone pain subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 | 2 / 40 (5.00%) 2 |
| Pain in extremity subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 6 | 2 / 34 (5.88%) 2 | 7 / 40 (17.50%) 10 |
| Musculoskeletal chest pain | | | |

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|------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Myalgia | | | |
| subjects affected / exposed | 5 / 64 (7.81%) | 2 / 34 (5.88%) | 6 / 40 (15.00%) |
| occurrences (all) | 5 | 3 | 8 |
| Muscle tightness | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 1 / 34 (2.94%) | 3 / 40 (7.50%) |
| occurrences (all) | 2 | 1 | 3 |
| Eye infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 34 (2.94%) | 1 / 40 (2.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 1 / 34 (2.94%) | 1 / 40 (2.50%) |
| occurrences (all) | 4 | 1 | 1 |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------------|-----------------|----------------|-----------------|
| Folliculitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 6 / 40 (15.00%) |
| occurrences (all) | 0 | 0 | 8 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 5 / 40 (12.50%) |
| occurrences (all) | 0 | 0 | 13 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 3 / 34 (8.82%) | 0 / 40 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | 1 / 34 (2.94%) | 1 / 40 (2.50%) |
| occurrences (all) | 10 | 1 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 3 / 34 (8.82%) | 3 / 40 (7.50%) |
| occurrences (all) | 2 | 3 | 4 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Febrile infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 34 (2.94%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 0 | 0 | 2 |

| | | | |
|------------------------------------|------------------|----------------|-----------------|
| Vulvitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Food craving | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 11 / 64 (17.19%) | 1 / 34 (2.94%) | 8 / 40 (20.00%) |
| occurrences (all) | 12 | 1 | 10 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 34 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 34 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 2 | 0 | 3 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 6 / 40 (15.00%) |
| occurrences (all) | 0 | 0 | 6 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 34 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 64 (6.25%) | 1 / 34 (2.94%) | 3 / 40 (7.50%) |
| occurrences (all) | 4 | 1 | 6 |
| Dehydration | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 2 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 1 / 34 (2.94%) 1 | 0 / 40 (0.00%) 0 |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 | 0 / 40 (0.00%) 0 |

| | | | |
|---|---------------------|--|--|
| Non-serious adverse events | Cohort 3 (IP) | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 6 / 6 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Melanocytic naevus subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Cancer pain subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Tumour associated fever subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Phlebitis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| General disorders and administration site conditions Face oedema subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |

| | | | |
|---|----------------|--|--|
| Asthenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | | |
| occurrences (all) | 6 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | | |
| occurrences (all) | 3 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | | |
| occurrences (all) | 2 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---------------------------------------|----------------|--|--|
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cough | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | | |
| occurrences (all) | 3 | | |
| Hiccups | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Insomnia | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Depression subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Product issues Device occlusion subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Amylase increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Ejection fraction decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Lipase increased | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 2 | | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Weight increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Cardiac murmur subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Blood potassium decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Body temperature increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---------------------|--|--|
| Infusion related reaction subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Lumbar vertebral fracture subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Sunburn subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Gastrointestinal stoma complication subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Stoma site pain subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Wound dehiscence subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Headache subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Peripheral motor neuropathy subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Neurotoxicity subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Paraesthesia | | | |

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 2 | | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 2 | | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 3 / 6 (50.00%) 7 | | |
| Polyneuropathy subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Restless legs syndrome subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Somnolence subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Taste disorder subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Sensory loss subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Ageusia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Neutropenia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |

| | | | |
|--|---|--|--|
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Ear and labyrinth disorders Auditory meatus external erosion subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Eye disorders Cataract subjects affected / exposed occurrences (all) Conjunctival haemorrhage subjects affected / exposed occurrences (all) Lacrimation increased subjects affected / exposed occurrences (all) Periorbital oedema subjects affected / exposed occurrences (all) Dry eye subjects affected / exposed occurrences (all) Visual impairment subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 | | |
| Gastrointestinal disorders Angular cheilitis subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation | 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 0 | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 2 / 6 (33.33%) | | |
| occurrences (all) | 2 | | |
| Dental cyst | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | | |
| occurrences (all) | 9 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | | |
| occurrences (all) | 2 | | |
| Palatal ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 2 | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry mouth | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Toothache subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Eructation subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Odynophagia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Cheilitis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Flatulence subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Anal haemorrhage subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Hepatobiliary disorders Hepatomegaly subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Dermatitis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Nail ridging | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Erythema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Onychoclasia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | | |
| occurrences (all) | 7 | | |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|-----------------------------|----------------|--|--|
| Rash macular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermal cyst | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rosacea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Erythema nodosum | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hair texture abnormal | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin exfoliation | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Hand dermatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---------------------|--|--|
| Blister subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Acne subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Proteinuria subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Renal colic subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | | |
| Back pain subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | | |

| | | | |
|-----------------------------|----------------|--|--|
| Bone pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle tightness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye infection | | | |

| | | | |
|-----------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Paronychia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vascular device infection | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Febrile infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vulvitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Food craving | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | | |
| occurrences (all) | 2 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|-----------------------------|----------------|--|--|
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | | |
| occurrences (all) | 1 | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 30 November 2015 | Changes include the replacement of terms "MPDL3280A" and "MPDL3280A (anti-PD-L1 antibody)" with "atezolizumab" (international, non-proprietary name); revision of study eligibility criteria to allow patients with cerebellar metastases, exclude patients with progression of CNS disease between last CNS-directed therapy and study baseline prior to baseline, exclude patients requiring steroid therapy for CNS disease; revision of Cohort 2 eligibility criteria to exclude patients continuing RANKL inhibitor therapy; clarifications and updates on drug products; updates to address any safety concerns or knowledge gaps; and other minor details. |
| 11 April 2016 | Changes include increasing the Cohort 2 target sample size from 330 to 405 patients to increase statistical power for Cohort 2 analyses and accommodate rapid accrual into Cohort 2. As a result of this change, the estimated duration of the study for Cohort 2 was increased from 17 to 22 months and the estimated overall study accrual was increased from 610 to 700 patients. |
| 24 November 2016 | Changes include Cohort 2 closure due to completion of accrual; incorporation of two new cohorts (Cohort 3: capecitabine/trastuzumab/pertuzumab vs fluoropyrimidine/bevacizumab in HER2+ patients; Cohort 4: cobimetinib/atezolizumab vs fluoropyrimidine/bevacizumab in HER2-/MSI-H; HER2-/MSS/BRAFwt or HER2-/MSS/BRAFmut/RASmut patients); adaptation of cohort assignment decision tree and study length estimates to accommodate new cohorts and Cohort 2 closure; removal of co-primary endpoint "early efficacy during the Maintenance Treatment Phase" based on advisory committees' advice (PFS remains as single primary efficacy endpoint); optional stool sample collection added to address a new exploratory microbiome biomarker evaluation objective; preliminary assessments of efficacy in each cohort removed based on advisory committees' advice; maximum allowable 5-FU dosing in Cohort 1 increased to 2,400 mg/m ² based on completion of safety run-in review by the iDMC; local ablation for liver metastases now allowed during the induction treatment phase; second-line treatment for BRAFmut early progressors modified to 5-FU/vemurafenib/cetuximab for BRAFmut/MSS patients and FP/bevacizumab/atezolizumab for BRAFmut/MSI-H patients; updates to cohort-specific exclusion criteria, safety monitoring, and treatment management based on current safety data. Country specific protocols versions introduced for Spain and France due to jurisdictional requirements for safety monitoring and for Egypt and the UK where Cohorts 3 and 4 were not opened (study enrolment closed in Egypt and UK). |
| 08 August 2018 | In accordance with independent Data Monitoring Committee recommendations following review of safety data, accrual into Cohort 4 was closed. |
| 19 December 2019 | Enrolment into study was closed. Cohort 4 (now closed due to iDMC recommendations) had broad biomarker eligibility criteria and was introduced to replace Cohort 2 (previously closed due to completion of accrual). No new or modified cohorts with broad eligibility criteria suitable for addition to protocol MO29112 were identified. Without a broad eligibility cohort to replace Cohort 4, the majority of patients eligible for study entry would not be eligible for any maintenance cohort assignment upon completion of study induction treatment. For this reason, the Sponsor decided to permanently discontinue enrolment. |
| 18 February 2020 | Changes include updates to safety information and treatment management for patients receiving atezolizumab; update to responsible Medical Monitor. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|--|----------------|
| 12 February 2018 | Following the iDMC review of cohort 4 data a temporary recruitment halt to the whole study and a temporary halt to randomisation into cohort 4 was undertaken. | 08 August 2018 |

Notes:

Limitations and caveats

None reported