



Clinical trial results:

A randomized discontinuation study of XL184 in subjects with advanced solid tumors

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2009-012964-14 |
| Trial protocol | BE GB |
| Global end of trial date | 23 June 2014 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 24 March 2022 |
| First version publication date | 24 March 2022 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | XL184-203 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00940225 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Exelixis, Inc. |
| Sponsor organisation address | 1851 Harbor Bay Parkway, Alameda, United States, 94502 |
| Public contact | Medical Information, Exelixis Inc, +1 866939 4041, |
| Scientific contact | Medical Information, Exelixis Inc, +1 866939 4041, |

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 | 30 May 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 May 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 June 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is:

- To evaluate the efficacy of XL184 in subjects with advanced solid tumors

Protection of trial subjects:

An independent data monitoring committee was in place to monitor safety during the randomized discontinuation portion of the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 02 September 2009 |
| 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 | United Kingdom: 15 |
| Country: Number of subjects enrolled | Belgium: 43 |
| Country: Number of subjects enrolled | Israel: 49 |
| Country: Number of subjects enrolled | Taiwan: 23 |
| Country: Number of subjects enrolled | United States: 600 |
| Worldwide total number of subjects | 730 |
| EEA total number of subjects | 43 |

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) | 403 |
| From 65 to 84 years | 314 |

Subject disposition

Recruitment

Recruitment details:

Enrollment into the Randomized Discontinuation Trial (RDT) Cohorts: September 2009 - July 2011.
Enrollment into the Non Randomized Expansion (NRE) Cohorts: February 2011 - April 2012.

Pre-assignment

Screening details:

Screening evaluations were completed prior to enrollment to determine the eligibility of subjects per protocol inclusion/exclusion criteria.

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | RDT Cohort - Castration Resistant Prostate Cancer |

Arm description: -

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

Dosage and administration details:

Administered orally, once daily, at the assigned dose

| | |
|------------------|-----------------------|
| Arm title | RDT Cohort - Melanoma |
|------------------|-----------------------|

Arm description: -

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

Dosage and administration details:

Administered orally, once daily, at the assigned dose

| | |
|------------------|---|
| Arm title | RDT Cohort - Non Small Cell Lung Cancer |
|------------------|---|

Arm description: -

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

Dosage and administration details:

Administered orally, once daily, at the assigned dose

| | |
|------------------|--------------------------------|
| Arm title | RDT Cohort - Pancreatic Cancer |
|------------------|--------------------------------|

| | |
|---|--|
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | cabozantinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered orally, once daily, at the assigned dose | |
| Arm title | RDT Cohort - Gastric/Gastroesophageal Cancer |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | cabozantinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered orally, once daily, at the assigned dose | |
| Arm title | RDT Cohort - Hepatocellular Carcinoma |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | cabozantinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered orally, once daily, at the assigned dose | |
| Arm title | RDT Cohort - Small Cell Lung Cancer |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | cabozantinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered orally, once daily, at the assigned dose | |
| Arm title | RDT Cohort - Ovarian Cancer |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | cabozantinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered orally, once daily, at the assigned dose | |
| Arm title | RDT Cohort - Metastatic Breast Cancer |

| | |
|--|---------------|
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | cabozantinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Administered orally, once daily, at the assigned dose

| | |
|------------------|--|
| Arm title | NRE Cohort - Castration Resistant Prostate Cancer (100 mg) |
|------------------|--|

| | |
|--|---------------|
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | cabozantinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Administered orally, once daily, at the assigned dose

| | |
|------------------|---|
| Arm title | NRE Cohort - Castration Resistant Prostate Cancer (40 mg) |
|------------------|---|

| | |
|--|---------------|
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | cabozantinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Administered orally, once daily, at the assigned dose

| | |
|------------------|-----------------------------|
| Arm title | NRE Cohort - Ovarian Cancer |
|------------------|-----------------------------|

| | |
|--|---------------|
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | cabozantinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Administered orally, once daily, at the assigned dose

| Number of subjects in period 1 | RDT Cohort - Castration Resistant Prostate Cancer | RDT Cohort - Melanoma | RDT Cohort - Non Small Cell Lung Cancer |
|---------------------------------------|---|--------------------------|---|
| Started | 171 | 77 | 60 |
| Completed | 171 | 77 | 60 |

| Number of subjects in period 1 | RDT Cohort - Pancreatic Cancer | RDT Cohort - Gastric/Gastroesoph | RDT Cohort - Hepatocellular |
|---------------------------------------|-----------------------------------|-------------------------------------|--------------------------------|
| | | | |

| | | | |
|-----------|----|--------------|-----------|
| | | ageal Cancer | Carcinoma |
| Started | 20 | 21 | 41 |
| Completed | 20 | 21 | 41 |

| Number of subjects in period 1 | RDT Cohort - Small Cell Lung Cancer | RDT Cohort - Ovarian Cancer | RDT Cohort - Metastatic Breast Cancer |
|--------------------------------|-------------------------------------|-----------------------------|---------------------------------------|
| | | | |
| Started | 21 | 70 | 45 |
| Completed | 21 | 70 | 45 |

| Number of subjects in period 1 | NRE Cohort - Castration Resistant Prostate Cancer (100 mg) | NRE Cohort - Castration Resistant Prostate Cancer (40 mg) | NRE Cohort - Ovarian Cancer |
|--------------------------------|--|---|-----------------------------|
| | | | |
| Started | 93 | 51 | 60 |
| Completed | 93 | 51 | 60 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|--|
| Reporting group title | RDT Cohort - Castration Resistant Prostate Cancer |
| Reporting group description: - | |
| Reporting group title | RDT Cohort - Melanoma |
| Reporting group description: - | |
| Reporting group title | RDT Cohort - Non Small Cell Lung Cancer |
| Reporting group description: - | |
| Reporting group title | RDT Cohort - Pancreatic Cancer |
| Reporting group description: - | |
| Reporting group title | RDT Cohort - Gastric/Gastroesophageal Cancer |
| Reporting group description: - | |
| Reporting group title | RDT Cohort - Hepatocellular Carcinoma |
| Reporting group description: - | |
| Reporting group title | RDT Cohort - Small Cell Lung Cancer |
| Reporting group description: - | |
| Reporting group title | RDT Cohort - Ovarian Cancer |
| Reporting group description: - | |
| Reporting group title | RDT Cohort - Metastatic Breast Cancer |
| Reporting group description: - | |
| Reporting group title | NRE Cohort - Castration Resistant Prostate Cancer (100 mg) |
| Reporting group description: - | |
| Reporting group title | NRE Cohort - Castration Resistant Prostate Cancer (40 mg) |
| Reporting group description: - | |
| Reporting group title | NRE Cohort - Ovarian Cancer |
| Reporting group description: - | |

| Reporting group values | RDT Cohort - Castration Resistant Prostate Cancer | RDT Cohort - Melanoma | RDT Cohort - Non Small Cell Lung Cancer |
|------------------------|---|-----------------------|---|
| Number of subjects | 171 | 77 | 60 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adult (18 - 65 years) | 64 | 39 | 27 |
| Adult (over 65 years) | 107 | 38 | 33 |
| Age continuous | | | |
| Units: years | | | |
| median | 68.0 | 65.0 | 66.0 |
| full range (min-max) | 47 to 88 | 30 to 90 | 36 to 87 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 171 | 35 | 27 |
| Male | 0 | 42 | 33 |

| Reporting group values | RDT Cohort - Pancreatic Cancer | RDT Cohort - Gastric/Gastroesophageal Cancer | RDT Cohort - Hepatocellular Carcinoma |
|------------------------|--------------------------------|--|---------------------------------------|
| Number of subjects | 20 | 21 | 41 |

| | | | |
|---------------------------------------|----------|----------|----------|
| Age categorical Units: Subjects | | | |
| Adult (18 - 65 years) | 13 | 13 | 29 |
| Adult (over 65 years) | 7 | 8 | 12 |
| Age continuous Units: years | | | |
| median | 63.0 | 62.0 | 60.0 |
| full range (min-max) | 40 to 78 | 40 to 80 | 32 to 82 |
| Gender categorical Units: Subjects | | | |
| Female | 7 | 5 | 10 |
| Male | 13 | 16 | 31 |

| | | | |
|---------------------------------------|-------------------------------------|-----------------------------|---------------------------------------|
| Reporting group values | RDT Cohort - Small Cell Lung Cancer | RDT Cohort - Ovarian Cancer | RDT Cohort - Metastatic Breast Cancer |
| Number of subjects | 21 | 70 | 45 |
| Age categorical Units: Subjects | | | |
| Adult (18 - 65 years) | 14 | 48 | 39 |
| Adult (over 65 years) | 7 | 22 | 6 |
| Age continuous Units: years | | | |
| median | 65.0 | 60.5 | 56.0 |
| full range (min-max) | 47 to 81 | 26 to 79 | 27 to 74 |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 70 | 44 |
| Male | 9 | 0 | 1 |

| | | | |
|---------------------------------------|--|---|-----------------------------|
| Reporting group values | NRE Cohort - Castration Resistant Prostate Cancer (100 mg) | NRE Cohort - Castration Resistant Prostate Cancer (40 mg) | NRE Cohort - Ovarian Cancer |
| Number of subjects | 93 | 51 | 60 |
| Age categorical Units: Subjects | | | |
| Adult (18 - 65 years) | 44 | 29 | 44 |
| Adult (over 65 years) | 49 | 22 | 16 |
| Age continuous Units: years | | | |
| median | 66.0 | 65.0 | 59.5 |
| full range (min-max) | 46 to 85 | 43 to 83 | 38 to 76 |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | 60 |
| Male | 93 | 51 | 0 |

| | | | |
|------------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 730 | | |
| Age categorical Units: Subjects | | | |
| Adult (18 - 65 years) | 403 | | |

| | | | |
|-----------------------|-----|--|--|
| Adult (over 65 years) | 327 | | |
|-----------------------|-----|--|--|

| | | | |
|--|-----|--|--|
| Age continuous Units: years median full range (min-max) | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 441 | | |
| Male | 289 | | |

End points

End points reporting groups

| | |
|------------------------------|--|
| Reporting group title | RDT Cohort - Castration Resistant Prostate Cancer |
| Reporting group description: | - |
| Reporting group title | RDT Cohort - Melanoma |
| Reporting group description: | - |
| Reporting group title | RDT Cohort - Non Small Cell Lung Cancer |
| Reporting group description: | - |
| Reporting group title | RDT Cohort - Pancreatic Cancer |
| Reporting group description: | - |
| Reporting group title | RDT Cohort - Gastric/Gastroesophageal Cancer |
| Reporting group description: | - |
| Reporting group title | RDT Cohort - Hepatocellular Carcinoma |
| Reporting group description: | - |
| Reporting group title | RDT Cohort - Small Cell Lung Cancer |
| Reporting group description: | - |
| Reporting group title | RDT Cohort - Ovarian Cancer |
| Reporting group description: | - |
| Reporting group title | RDT Cohort - Metastatic Breast Cancer |
| Reporting group description: | - |
| Reporting group title | NRE Cohort - Castration Resistant Prostate Cancer (100 mg) |
| Reporting group description: | - |
| Reporting group title | NRE Cohort - Castration Resistant Prostate Cancer (40 mg) |
| Reporting group description: | - |
| Reporting group title | NRE Cohort - Ovarian Cancer |
| Reporting group description: | - |

Primary: Objective Response Rate (ORR)

| | |
|------------------------|---|
| End point title | Objective Response Rate (ORR) ^{[1][2]} |
| End point description: | |
| End point type | Primary |
| End point timeframe: | assessed every 6 weeks until radiographic disease progression, and analyzed at the time of the primary analysis |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive endpoint (single arm, no across-arm comparison)

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoint was only assessed for certain tumor types.

| End point values | RDT Cohort - Castration Resistant Prostate Cancer | RDT Cohort - Melanoma | RDT Cohort - Non Small Cell Lung Cancer | RDT Cohort - Pancreatic Cancer |
|----------------------------------|---|-----------------------|---|--------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 171 | 77 | 60 | 20 |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 4.7 (2.0 to 8.7) | 5.2 (1.8 to 12.4) | 10.0 (4.4 to 20.3) | 0 (0 to 15.4) |

| End point values | RDT Cohort - Gastric/Gastroesophageal Cancer | RDT Cohort - Hepatocellular Carcinoma | RDT Cohort - Small Cell Lung Cancer | RDT Cohort - Ovarian Cancer |
|----------------------------------|--|---------------------------------------|-------------------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 41 | 21 | 70 |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 4.8 (0.2 to 21.8) | 4.9 (0.9 to 16.1) | 4.8 (0.2 to 21.8) | 21.7 (13.1 to 32.4) |

| End point values | RDT Cohort - Metastatic Breast Cancer | NRE Cohort - Ovarian Cancer | | |
|----------------------------------|---------------------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 60 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 10.0 (6.0 to 25.7) | 10.0 (3.3 to 21.8) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Bone scan response

End point title | Bone scan response^[3]^[4]

End point description:

End point type | Primary

End point timeframe:

Assessed approximately every 6 weeks using MRI, CT, and/or bone scans

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive endpoint (single arm, no across-arm comparison)

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: End point was only appropriate for prostate cancer, and was only prospectively measured in the two NRE cohorts.

| | | | | |
|----------------------------------|--|---|--|--|
| End point values | NRE Cohort - Castration Resistant Prostate Cancer (100 mg) | NRE Cohort - Castration Resistant Prostate Cancer (40 mg) | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 | 51 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 74.2 (64.1 to 82.7) | 47.1 (32.9 to 61.5) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival

| | |
|-----------------|---|
| End point title | Progression Free Survival ^{[5][6]} |
|-----------------|---|

End point description:

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

End point timeframe:

Assessed approximately every 6 weeks using MRI/CT until progressive disease

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive endpoint (single arm, no across-arm comparison)

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoint was only assessed for certain tumor types.

| | | | | |
|----------------------------------|---|-----------------------|---|--------------------------------|
| End point values | RDT Cohort - Castration Resistant Prostate Cancer | RDT Cohort - Melanoma | RDT Cohort - Non Small Cell Lung Cancer | RDT Cohort - Pancreatic Cancer |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 171 | 77 | 60 | 20 |
| Units: months | | | | |
| median (confidence interval 95%) | 6.8 (3.9 to 9.7) | 2.8 (1.4 to 6.9) | 4.0 (1.4 to 5.7) | 2.7 (1.3 to 5.5) |

| | | | | |
|----------------------------------|--|---------------------------------------|-------------------------------------|-----------------------------|
| End point values | RDT Cohort - Gastric/Gastroesophageal Cancer | RDT Cohort - Hepatocellular Carcinoma | RDT Cohort - Small Cell Lung Cancer | RDT Cohort - Ovarian Cancer |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 41 | 21 | 70 |
| Units: months | | | | |
| median (confidence interval 95%) | 1.4 (1.3 to 1.4) | 5.2 (3.6 to 9.3) | 3.4 (1.4 to 8.2) | 5.5 (2.7 to 11.0) |

| | | | | |
|----------------------------------|---|--|--|--|
| End point values | RDT Cohort - Metastatic Breast Cancer | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 45 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.3 (1.4 to 8.1) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed at regular study visits from baseline until discontinuation from study, through to the date of the primary analysis.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | RDT - All Cohorts |
|-----------------------|-------------------|

Reporting group description:

Includes subjects in all 9 of the RDT cohorts.

| | |
|-----------------------|--------------------------|
| Reporting group title | NRE Cohort - CRPC 100 mg |
|-----------------------|--------------------------|

Reporting group description: -

| | |
|-----------------------|-------------------------|
| Reporting group title | NRE Cohort - CRPC 40 mg |
|-----------------------|-------------------------|

Reporting group description: -

| | |
|-----------------------|-----------------------------|
| Reporting group title | NRE Cohort - Ovarian Cancer |
|-----------------------|-----------------------------|

Reporting group description: -

| Serious adverse events | RDT - All Cohorts | NRE Cohort - CRPC 100 mg | NRE Cohort - CRPC 40 mg |
|---|--------------------|--------------------------|-------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 223 / 526 (42.40%) | 53 / 93 (56.99%) | 30 / 51 (58.82%) |
| number of deaths (all causes) | 54 | 12 | 12 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Intracranial tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Malignant pleural effusion | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| metastases to the central nervous system | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| metastatic pain | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 1 / 93 (1.08%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Ovarian cancer | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 3 / 93 (3.23%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of the oral cavity | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Vascular disorders | | | |
| Bleeding varicose vein | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |

| | | | |
|---|------------------|----------------|----------------|
| Deep vein thrombosis | | | |
| subjects affected / exposed | 12 / 526 (2.28%) | 1 / 93 (1.08%) | 2 / 51 (3.92%) |
| occurrences causally related to treatment / all | 5 / 12 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Hypertension | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | 0 / 93 (0.00%) | 0 / 51 (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 | 5 / 526 (0.95%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 venous thrombosis | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Venous stenosis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| 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 | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Asthenia | | | |
| subjects affected / exposed | 9 / 526 (1.71%) | 1 / 93 (1.08%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 2 / 9 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Death | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Drug withdrawal syndrome | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 | 2 / 526 (0.38%) | 5 / 93 (5.38%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 5 / 526 (0.95%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| multi-organ failure | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Pain | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Performance status decreased | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| 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 | 5 / 526 (0.95%) | 2 / 93 (2.15%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| 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 | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Bronchopleural fistula | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 526 (1.52%) | 4 / 93 (4.30%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 8 | 2 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 2 / 93 (2.15%) | 0 / 51 (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 |
| Pleural effusion | | | |
| subjects affected / exposed | 6 / 526 (1.14%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary alveolar haemorrhage | | | |

| | | | |
|---|------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 23 / 526 (4.37%) | 7 / 93 (7.53%) | 8 / 51 (15.69%) |
| occurrences causally related to treatment / all | 16 / 23 | 6 / 7 | 7 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 distress | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 | 7 / 526 (1.33%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Confusional state | | | |
| subjects affected / exposed | 6 / 526 (1.14%) | 2 / 93 (2.15%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |
| subjects affected / exposed | 9 / 526 (1.71%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |

| | | | |
|---|-----------------|----------------|----------------|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| 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 | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 sodium decreased | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| 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 uric acid increased | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| 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 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Transaminases increased | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| 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 | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| laceration | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Radiation pneumonitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 compression fracture | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| 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 | 1 / 526 (0.19%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Wound dehiscence | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| 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 | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| tachycardia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 | 8 / 526 (1.52%) | 4 / 93 (4.30%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 arrest | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 failure congestive | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Cardiac tamponade | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| pericardial effusion | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| 6th nerve paralysis | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| convulsion | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Headache | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Haemorrhage intracranial | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| 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 encephalopathy | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Occipital neuralgia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Speech disorder | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 1 / 93 (1.08%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural effusion | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Syncope | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 526 (0.57%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| idiopathic thrombocytopenia purpura | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Corneal epithelium defect | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Macular oedema | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Parophthalmia | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| 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 pain | | | |
| subjects affected / exposed | 9 / 526 (1.71%) | 2 / 93 (2.15%) | 2 / 51 (3.92%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 fissure | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Anal ulcer | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Ascites | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Colitis | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 2 / 93 (2.15%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 15 / 526 (2.85%) | 2 / 93 (2.15%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 11 / 15 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticular perforation | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Dyspepsia | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Enterocutaneous fistula | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Enterovesical fistula | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 5 / 526 (0.95%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Haemorrhoids | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inflammatory bowel disease | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 | 3 / 526 (0.57%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Intestinal perforation | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Nausea | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 12 / 526 (2.28%) | 9 / 93 (9.68%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 10 / 12 | 6 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction gastric | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Pancreatitis | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| peritoneal haemorrhage | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Rectal haemorrhage | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Rectal obstruction | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Rectal stenosis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 5 / 526 (0.95%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Vomiting | | | |
| subjects affected / exposed | 15 / 526 (2.85%) | 7 / 93 (7.53%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 10 / 15 | 3 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Hepatobiliary disorders | | | |
| bile duct obstruction | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 2 / 51 (3.92%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Hepatic failure | | | |
| subjects affected / exposed | 5 / 526 (0.95%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 2 / 93 (2.15%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Palmar-plantar erythrodysesthesia syndrome | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 pruritic | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Renal and urinary disorders | | | |
| acute prerenal failure | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Haematuria | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Haemorrhage urinary tract | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Hydronephrosis | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | 1 / 93 (1.08%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 5 / 526 (0.95%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| renal failure acute | | | |
| subjects affected / exposed | 11 / 526 (2.09%) | 4 / 93 (4.30%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 11 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric obstruction | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethral obstruction | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Hypopituitarism | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| 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 | 5 / 526 (0.95%) | 5 / 93 (5.38%) | 4 / 51 (7.84%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 6 / 93 (6.45%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Flank pain | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Groin pain | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| 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 disc protrusion | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Muscular weakness | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | 1 / 93 (1.08%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 2 / 93 (2.15%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 2 / 93 (2.15%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 1 / 93 (1.08%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic foot infection | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Douglas' abscess | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Empyema | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 viral | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Herpes oesophagitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Klebsiella bacteraemia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| lung infection | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Otitis media | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 1 / 526 (0.19%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Pelvic abscess | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Perirectal abscess | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 16 / 526 (3.04%) | 3 / 93 (3.23%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Pneumonia fungal | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (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 |
| Rectal abscess | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Sepsis | | | |
| subjects affected / exposed | 5 / 526 (0.95%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 526 (1.33%) | 5 / 93 (5.38%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Wound sepsis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 17 / 526 (3.23%) | 6 / 93 (6.45%) | 2 / 51 (3.92%) |
| occurrences causally related to treatment / all | 7 / 17 | 4 / 6 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Failure to thrive | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | 2 / 93 (2.15%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | 0 / 93 (0.00%) | 0 / 51 (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 | 1 / 526 (0.19%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| 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 | 5 / 526 (0.95%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | 0 / 93 (0.00%) | 0 / 51 (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 |
| Hyponatraemia | | | |
| subjects affected / exposed | 7 / 526 (1.33%) | 2 / 93 (2.15%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 4 / 7 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| 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 | NRE Cohort - Ovarian Cancer | | |
|--|-----------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 34 / 60 (56.67%) | | |
| number of deaths (all causes) | 11 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intracranial tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| metastases to the central nervous system | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| metastatic pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cancer | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of the oral cavity | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Bleeding varicose vein | | | |
| subjects affected / exposed | 0 / 60 (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 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematoma | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhage | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypertension | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypotension | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypovolaemic shock | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lymphoedema | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Orthostatic hypotension | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pelvic venous thrombosis | | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous stenosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug withdrawal syndrome | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Malaise | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| multi-organ failure | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Performance status decreased | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchopleural fistula | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary alveolar haemorrhage | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |

| | | | | |
|---|----------------|--|--|--|
| Alanine aminotransferase increased | | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Amylase increased | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aspartate aminotransferase increased | | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood sodium decreased | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood uric acid increased | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lipase increased | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Liver function test abnormal | | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Platelet count decreased | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transaminases increased | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| laceration | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radiation pneumonitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound dehiscence | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| tachycardia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 60 (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 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| pericardial effusion | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| 6th nerve paralysis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| convulsion | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage intracranial | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Occipital neuralgia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural effusion | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (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 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| idiopathic thrombocytopenia purpura | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 60 (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 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Corneal epithelium defect | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Macular oedema | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Parophthalmia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 7 / 60 (11.67%) | | |
| occurrences causally related to treatment / all | 1 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal fistula | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal ulcer | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticular perforation | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspepsia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocutaneous fistula | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterovesical fistula | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoids | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inflammatory bowel disease | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 60 (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 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Melaena | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 8 / 60 (13.33%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| peritoneal haemorrhage | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal obstruction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal stenosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 11 / 60 (18.33%) | | |
| occurrences causally related to treatment / all | 0 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| bile duct obstruction | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 60 (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 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| acute prerenal failure | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage urinary tract | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| renal failure acute | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urethral obstruction | | | |
| subjects affected / exposed | 0 / 60 (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 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypopituitarism | | | |
| subjects affected / exposed | 0 / 60 (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 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|----------------|--|--|--|
| Back pain | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bone pain | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Flank pain | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Groin pain | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral disc protrusion | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Muscle haemorrhage | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Muscular weakness | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal chest pain | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neck pain | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Bronchitis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 60 (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 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic foot infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Douglas' abscess | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Empyema | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Herpes oesophagitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Klebsiella bacteraemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| lung infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis media | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic abscess | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia fungal | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 60 (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 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound sepsis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 2 / 60 (3.33%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gout | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | RDT - All Cohorts | NRE Cohort - CRPC 100 mg | NRE Cohort - CRPC 40 mg |
|--|--------------------|-----------------------------|----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 524 / 526 (99.62%) | 93 / 93 (100.00%) | 51 / 51 (100.00%) |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 6 / 93 (6.45%) | 4 / 51 (7.84%) |
| occurrences (all) | 0 | 6 | 4 |
| Hot flush | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 5 / 93 (5.38%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 127 / 526 (24.14%) | 25 / 93 (26.88%) | 10 / 51 (19.61%) |
| occurrences (all) | 127 | 25 | 10 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 11 / 93 (11.83%) | 2 / 51 (3.92%) |
| occurrences (all) | 0 | 11 | 2 |
| Pallor | | | |

| | | | |
|--|--------------------|------------------|------------------|
| subjects affected / exposed | 0 / 526 (0.00%) | 7 / 93 (7.53%) | 1 / 51 (1.96%) |
| occurrences (all) | 0 | 7 | 1 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 118 / 526 (22.43%) | 18 / 93 (19.35%) | 7 / 51 (13.73%) |
| occurrences (all) | 118 | 18 | 7 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 1 | 3 |
| Chills | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 5 / 93 (5.38%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 78 / 526 (14.83%) | 13 / 93 (13.98%) | 11 / 51 (21.57%) |
| occurrences (all) | 78 | 13 | 11 |
| Fatigue | | | |
| subjects affected / exposed | 345 / 526 (65.59%) | 77 / 93 (82.80%) | 32 / 51 (62.75%) |
| occurrences (all) | 345 | 77 | 32 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 84 / 526 (15.97%) | 14 / 93 (15.05%) | 8 / 51 (15.69%) |
| occurrences (all) | 84 | 14 | 8 |
| Pain | | | |
| subjects affected / exposed | 38 / 526 (7.22%) | 6 / 93 (6.45%) | 6 / 51 (11.76%) |
| occurrences (all) | 38 | 6 | 6 |
| Pyrexia | | | |
| subjects affected / exposed | 50 / 526 (9.51%) | 7 / 93 (7.53%) | 1 / 51 (1.96%) |
| occurrences (all) | 50 | 7 | 1 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 5 / 93 (5.38%) | 2 / 51 (3.92%) |
| occurrences (all) | 0 | 5 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-----------------------------|--------------------|------------------|------------------|
| Cough | | | |
| subjects affected / exposed | 88 / 526 (16.73%) | 14 / 93 (15.05%) | 3 / 51 (5.88%) |
| occurrences (all) | 88 | 14 | 3 |
| Dysphonia | | | |
| subjects affected / exposed | 142 / 526 (27.00%) | 34 / 93 (36.56%) | 9 / 51 (17.65%) |
| occurrences (all) | 142 | 34 | 9 |
| Dyspnoea | | | |
| subjects affected / exposed | 109 / 526 (20.72%) | 30 / 93 (32.26%) | 13 / 51 (25.49%) |
| occurrences (all) | 109 | 30 | 13 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 5 / 93 (5.38%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 5 | 3 |
| Epistaxis | | | |
| subjects affected / exposed | 36 / 526 (6.84%) | 7 / 93 (7.53%) | 1 / 51 (1.96%) |
| occurrences (all) | 36 | 7 | 1 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 5 / 93 (5.38%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 60 / 526 (11.41%) | 3 / 93 (3.23%) | 4 / 51 (7.84%) |
| occurrences (all) | 60 | 3 | 4 |
| Pleural effusion | | | |
| subjects affected / exposed | 28 / 526 (5.32%) | 8 / 93 (8.60%) | 1 / 51 (1.96%) |
| occurrences (all) | 28 | 8 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 3 / 93 (3.23%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 29 / 526 (5.51%) | 8 / 93 (8.60%) | 9 / 51 (17.65%) |
| occurrences (all) | 29 | 8 | 9 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 34 / 526 (6.46%) | 3 / 93 (3.23%) | 1 / 51 (1.96%) |
| occurrences (all) | 34 | 3 | 1 |
| Confusional state | | | |

| | | | |
|---|-------------------|------------------|----------------|
| subjects affected / exposed | 38 / 526 (7.22%) | 8 / 93 (8.60%) | 0 / 51 (0.00%) |
| occurrences (all) | 38 | 8 | 0 |
| Depression | | | |
| subjects affected / exposed | 38 / 526 (7.22%) | 4 / 93 (4.30%) | 2 / 51 (3.92%) |
| occurrences (all) | 38 | 4 | 2 |
| Insomnia | | | |
| subjects affected / exposed | 44 / 526 (8.37%) | 7 / 93 (7.53%) | 2 / 51 (3.92%) |
| occurrences (all) | 44 | 7 | 2 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 71 / 526 (13.50%) | 7 / 93 (7.53%) | 3 / 51 (5.88%) |
| occurrences (all) | 71 | 7 | 3 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 94 / 526 (17.87%) | 10 / 93 (10.75%) | 5 / 51 (9.80%) |
| occurrences (all) | 94 | 10 | 5 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 2 / 93 (2.15%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 2 | 3 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 2 / 93 (2.15%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 2 | 3 |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 2 / 93 (2.15%) | 1 / 51 (1.96%) |
| occurrences (all) | 0 | 2 | 1 |
| Haemoglobin decreased | | | |

| | | | |
|--|---------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 5 / 93 (5.38%) 5 | 2 / 51 (3.92%) 2 |
| Lipase increased subjects affected / exposed occurrences (all) | 35 / 526 (6.65%) 35 | 2 / 93 (2.15%) 2 | 1 / 51 (1.96%) 1 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 6 / 93 (6.45%) 6 | 0 / 51 (0.00%) 0 |
| Transaminases increased subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 3 / 93 (3.23%) 3 | 0 / 51 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 165 / 526 (31.37%) 165 | 42 / 93 (45.16%) 42 | 19 / 51 (37.25%) 19 |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 2 / 93 (2.15%) 2 | 1 / 51 (1.96%) 1 |
| Nervous system disorders Cognitive disorder subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 1 / 93 (1.08%) 1 | 2 / 51 (3.92%) 2 |
| Dizziness subjects affected / exposed occurrences (all) | 87 / 526 (16.54%) 87 | 15 / 93 (16.13%) 15 | 7 / 51 (13.73%) 7 |
| Dysgeusia subjects affected / exposed occurrences (all) | 156 / 526 (29.66%) 156 | 35 / 93 (37.63%) 35 | 14 / 51 (27.45%) 14 |
| Headache subjects affected / exposed occurrences (all) | 80 / 526 (15.21%) 80 | 13 / 93 (13.98%) 13 | 8 / 51 (15.69%) 8 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 3 / 93 (3.23%) 3 | 5 / 51 (9.80%) 5 |
| Neuropathy peripheral | | | |

| | | | |
|---|-------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 38 / 526 (7.22%) 38 | 7 / 93 (7.53%) 7 | 0 / 51 (0.00%) 0 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 5 / 93 (5.38%) 5 | 2 / 51 (3.92%) 2 |
| Syncope subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 2 / 93 (2.15%) 2 | 1 / 51 (1.96%) 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 66 / 526 (12.55%) 66 | 30 / 93 (32.26%) 30 | 6 / 51 (11.76%) 6 |
| Leukopenia subjects affected / exposed occurrences (all) | 27 / 526 (5.13%) 27 | 7 / 93 (7.53%) 7 | 3 / 51 (5.88%) 3 |
| Neutropenia subjects affected / exposed occurrences (all) | 35 / 526 (6.65%) 35 | 8 / 93 (8.60%) 8 | 3 / 51 (5.88%) 3 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 58 / 526 (11.03%) 58 | 10 / 93 (10.75%) 10 | 4 / 51 (7.84%) 4 |
| Eye disorders | | | |
| Dry eye subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 1 / 93 (1.08%) 1 | 1 / 51 (1.96%) 1 |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 2 / 93 (2.15%) 2 | 4 / 51 (7.84%) 4 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 0 / 93 (0.00%) 0 | 0 / 51 (0.00%) 0 |
| Abdominal distension subjects affected / exposed occurrences (all) | 31 / 526 (5.89%) 31 | 4 / 93 (4.30%) 4 | 3 / 51 (5.88%) 3 |
| Abdominal pain | | | |

| | | | |
|----------------------------------|--------------------|------------------|------------------|
| subjects affected / exposed | 126 / 526 (23.95%) | 18 / 93 (19.35%) | 9 / 51 (17.65%) |
| occurrences (all) | 126 | 18 | 9 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 52 / 526 (9.89%) | 6 / 93 (6.45%) | 3 / 51 (5.88%) |
| occurrences (all) | 52 | 6 | 3 |
| Ascites | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 8 / 93 (8.60%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 8 | 3 |
| Constipation | | | |
| subjects affected / exposed | 171 / 526 (32.51%) | 33 / 93 (35.48%) | 16 / 51 (31.37%) |
| occurrences (all) | 171 | 33 | 16 |
| Diarrhoea | | | |
| subjects affected / exposed | 317 / 526 (60.27%) | 66 / 93 (70.97%) | 23 / 51 (45.10%) |
| occurrences (all) | 317 | 66 | 23 |
| Dry mouth | | | |
| subjects affected / exposed | 87 / 526 (16.54%) | 9 / 93 (9.68%) | 4 / 51 (7.84%) |
| occurrences (all) | 87 | 9 | 4 |
| Dyspepsia | | | |
| subjects affected / exposed | 64 / 526 (12.17%) | 12 / 93 (12.90%) | 7 / 51 (13.73%) |
| occurrences (all) | 64 | 12 | 7 |
| Dysphagia | | | |
| subjects affected / exposed | 38 / 526 (7.22%) | 6 / 93 (6.45%) | 0 / 51 (0.00%) |
| occurrences (all) | 38 | 6 | 0 |
| Early satiety | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 1 / 51 (1.96%) |
| occurrences (all) | 0 | 0 | 1 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 1 / 51 (1.96%) |
| occurrences (all) | 0 | 1 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 33 / 526 (6.27%) | 8 / 93 (8.60%) | 3 / 51 (5.88%) |
| occurrences (all) | 33 | 8 | 3 |
| Gastrooesophageal reflux disease | | | |

| | | | |
|--|--------------------|------------------|------------------|
| subjects affected / exposed | 46 / 526 (8.75%) | 6 / 93 (6.45%) | 5 / 51 (9.80%) |
| occurrences (all) | 46 | 6 | 5 |
| Glossodynia | | | |
| subjects affected / exposed | 42 / 526 (7.98%) | 2 / 93 (2.15%) | 3 / 51 (5.88%) |
| occurrences (all) | 42 | 2 | 3 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 2 / 93 (2.15%) | 2 / 51 (3.92%) |
| occurrences (all) | 0 | 2 | 2 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 1 | 3 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 273 / 526 (51.90%) | 66 / 93 (70.97%) | 30 / 51 (58.82%) |
| occurrences (all) | 273 | 66 | 30 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 6 / 93 (6.45%) | 1 / 51 (1.96%) |
| occurrences (all) | 0 | 6 | 1 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 99 / 526 (18.82%) | 15 / 93 (16.13%) | 5 / 51 (9.80%) |
| occurrences (all) | 99 | 15 | 5 |
| Toothache | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 1 / 51 (1.96%) |
| occurrences (all) | 0 | 1 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 196 / 526 (37.26%) | 39 / 93 (41.94%) | 19 / 51 (37.25%) |
| occurrences (all) | 196 | 39 | 19 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 43 / 526 (8.17%) | 1 / 93 (1.08%) | 0 / 51 (0.00%) |
| occurrences (all) | 43 | 1 | 0 |

| | | | |
|--|--------------------|------------------|-----------------|
| Dry skin | | | |
| subjects affected / exposed | 54 / 526 (10.27%) | 6 / 93 (6.45%) | 4 / 51 (7.84%) |
| occurrences (all) | 54 | 6 | 4 |
| Hair colour changes | | | |
| subjects affected / exposed | 53 / 526 (10.08%) | 4 / 93 (4.30%) | 0 / 51 (0.00%) |
| occurrences (all) | 53 | 4 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 1 / 93 (1.08%) | 2 / 51 (3.92%) |
| occurrences (all) | 0 | 1 | 2 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 179 / 526 (34.03%) | 24 / 93 (25.81%) | 7 / 51 (13.73%) |
| occurrences (all) | 179 | 24 | 7 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 4 / 93 (4.30%) | 1 / 51 (1.96%) |
| occurrences (all) | 0 | 4 | 1 |
| Rash | | | |
| subjects affected / exposed | 102 / 526 (19.39%) | 19 / 93 (20.43%) | 6 / 51 (11.76%) |
| occurrences (all) | 102 | 19 | 6 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 27 / 526 (5.13%) | 3 / 93 (3.23%) | 4 / 51 (7.84%) |
| occurrences (all) | 27 | 3 | 4 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 3 / 93 (3.23%) | 6 / 51 (11.76%) |
| occurrences (all) | 0 | 3 | 6 |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 0 / 93 (0.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 0 | 3 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 526 (0.00%) | 6 / 93 (6.45%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 6 | 3 |
| Proteinuria | | | |
| subjects affected / exposed | 34 / 526 (6.46%) | 0 / 93 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 34 | 0 | 0 |
| renal failure acute | | | |

| | | | |
|---|-------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 5 / 93 (5.38%) 5 | 1 / 51 (1.96%) 1 |
| Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 3 / 93 (3.23%) 3 | 4 / 51 (7.84%) 4 |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 66 / 526 (12.55%) 66 | 30 / 93 (32.26%) 30 | 4 / 51 (7.84%) 4 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 39 / 526 (7.41%) 39 | 29 / 93 (31.18%) 29 | 6 / 51 (11.76%) 6 |
| Back pain subjects affected / exposed occurrences (all) | 79 / 526 (15.02%) 79 | 30 / 93 (32.26%) 30 | 15 / 51 (29.41%) 15 |
| Bone pain subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 16 / 93 (17.20%) 16 | 7 / 51 (13.73%) 7 |
| Flank pain subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 5 / 93 (5.38%) 5 | 1 / 51 (1.96%) 1 |
| Groin pain subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 2 / 93 (2.15%) 2 | 3 / 51 (5.88%) 3 |
| Muscle spasms subjects affected / exposed occurrences (all) | 56 / 526 (10.65%) 56 | 10 / 93 (10.75%) 10 | 9 / 51 (17.65%) 9 |
| Muscular weakness subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 13 / 93 (13.98%) 13 | 7 / 51 (13.73%) 7 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 27 / 526 (5.13%) 27 | 13 / 93 (13.98%) 13 | 4 / 51 (7.84%) 4 |
| Musculoskeletal pain | | | |

| | | | |
|---|---------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 34 / 526 (6.46%) 34 | 21 / 93 (22.58%) 21 | 7 / 51 (13.73%) 7 |
| Myalgia subjects affected / exposed occurrences (all) | 36 / 526 (6.84%) 36 | 9 / 93 (9.68%) 9 | 1 / 51 (1.96%) 1 |
| Neck pain subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 4 / 93 (4.30%) 4 | 4 / 51 (7.84%) 4 |
| Pain in extremity subjects affected / exposed occurrences (all) | 90 / 526 (17.11%) 90 | 29 / 93 (31.18%) 29 | 12 / 51 (23.53%) 12 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 0 / 93 (0.00%) 0 | 0 / 51 (0.00%) 0 |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 6 / 93 (6.45%) 6 | 1 / 51 (1.96%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 4 / 93 (4.30%) 4 | 3 / 51 (5.88%) 3 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 64 / 526 (12.17%) 64 | 9 / 93 (9.68%) 9 | 4 / 51 (7.84%) 4 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 271 / 526 (51.52%) 271 | 70 / 93 (75.27%) 70 | 23 / 51 (45.10%) 23 |
| Dehydration subjects affected / exposed occurrences (all) | 84 / 526 (15.97%) 84 | 22 / 93 (23.66%) 22 | 5 / 51 (9.80%) 5 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 3 / 93 (3.23%) 3 | 1 / 51 (1.96%) 1 |
| Hypoalbuminaemia | | | |

| | | | |
|---|-------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 1 / 93 (1.08%) 1 | 1 / 51 (1.96%) 1 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 6 / 93 (6.45%) 6 | 2 / 51 (3.92%) 2 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 64 / 526 (12.17%) 64 | 14 / 93 (15.05%) 14 | 6 / 51 (11.76%) 6 |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 70 / 526 (13.31%) 70 | 6 / 93 (6.45%) 6 | 3 / 51 (5.88%) 3 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 30 / 526 (5.70%) 30 | 7 / 93 (7.53%) 7 | 3 / 51 (5.88%) 3 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 41 / 526 (7.79%) 41 | 5 / 93 (5.38%) 5 | 3 / 51 (5.88%) 3 |
| Malnutrition subjects affected / exposed occurrences (all) | 0 / 526 (0.00%) 0 | 0 / 93 (0.00%) 0 | 1 / 51 (1.96%) 1 |

| Non-serious adverse events | NRE Cohort - Ovarian Cancer | | |
|--|--------------------------------|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 60 / 60 (100.00%) | | |
| Vascular disorders Deep vein thrombosis subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | | |
| Hot flush subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | | |
| Hypertension subjects affected / exposed occurrences (all) | 19 / 60 (31.67%) 19 | | |
| Hypotension | | | |

| | | | |
|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | | |
| Pallor subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | | |
| Thrombosis subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 10 / 60 (16.67%) 10 | | |
| Chest discomfort subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | | |
| Chills subjects affected / exposed occurrences (all) | 5 / 60 (8.33%) 5 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 7 / 60 (11.67%) 7 | | |
| Fatigue subjects affected / exposed occurrences (all) | 47 / 60 (78.33%) 47 | | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 10 / 60 (16.67%) 10 | | |
| Pain subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 4 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 6 / 60 (10.00%) 6 | | |
| Spinal pain | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 11 / 60 (18.33%) | | |
| occurrences (all) | 11 | | |
| Dysphonia | | | |
| subjects affected / exposed | 16 / 60 (26.67%) | | |
| occurrences (all) | 16 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 11 / 60 (18.33%) | | |
| occurrences (all) | 11 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | | |
| occurrences (all) | 2 | | |
| Epistaxis | | | |
| subjects affected / exposed | 7 / 60 (11.67%) | | |
| occurrences (all) | 7 | | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 11 / 60 (18.33%) | | |
| occurrences (all) | 11 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences (all) | 4 | | |
| Productive cough | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences (all) | 4 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | | |
| occurrences (all) | 2 | | |
| Psychiatric disorders | | | |

| | | | |
|---|------------------|--|--|
| Anxiety | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | | |
| occurrences (all) | 8 | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | | |
| occurrences (all) | 2 | | |
| Depression | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences (all) | 4 | | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences (all) | 4 | | |
| Sleep disorder | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences (all) | 3 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 16 / 60 (26.67%) | | |
| occurrences (all) | 16 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 21 / 60 (35.00%) | | |
| occurrences (all) | 21 | | |
| Blood albumin decreased | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences (all) | 3 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 11 / 60 (18.33%) | | |
| occurrences (all) | 11 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | | |
| occurrences (all) | 2 | | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences (all) | 4 | | |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 7 / 60 (11.67%) 7 | | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | | |
| Lipase increased subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | | |
| Transaminases increased subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 18 / 60 (30.00%) 18 | | |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | | |
| Nervous system disorders Cognitive disorder subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | | |
| Dizziness subjects affected / exposed occurrences (all) | 18 / 60 (30.00%) 18 | | |
| Dysgeusia subjects affected / exposed occurrences (all) | 21 / 60 (35.00%) 21 | | |
| Headache subjects affected / exposed occurrences (all) | 17 / 60 (28.33%) 17 | | |
| Hypoaesthesia | | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 6 / 60 (10.00%) 6 | | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | | |
| Syncope subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 10 / 60 (16.67%) 10 | | |
| Leukopenia subjects affected / exposed occurrences (all) | 5 / 60 (8.33%) 5 | | |
| Neutropenia subjects affected / exposed occurrences (all) | 7 / 60 (11.67%) 7 | | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 9 / 60 (15.00%) 9 | | |
| Eye disorders | | | |
| Dry eye subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | | |
| Vision blurred subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 4 | | |
| Abdominal distension | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 10 / 60 (16.67%) | | |
| occurrences (all) | 10 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 28 / 60 (46.67%) | | |
| occurrences (all) | 28 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 7 / 60 (11.67%) | | |
| occurrences (all) | 7 | | |
| Ascites | | | |
| subjects affected / exposed | 6 / 60 (10.00%) | | |
| occurrences (all) | 6 | | |
| Chest pain | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences (all) | 3 | | |
| Constipation | | | |
| subjects affected / exposed | 22 / 60 (36.67%) | | |
| occurrences (all) | 22 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 47 / 60 (78.33%) | | |
| occurrences (all) | 47 | | |
| Dry mouth | | | |
| subjects affected / exposed | 12 / 60 (20.00%) | | |
| occurrences (all) | 12 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 15 / 60 (25.00%) | | |
| occurrences (all) | 15 | | |
| Dysphagia | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | | |
| occurrences (all) | 8 | | |
| Early satiety | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences (all) | 3 | | |
| Oesophagitis | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences (all) | 4 | | |
| Flatulence | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 5 / 60 (8.33%) | | |
| occurrences (all) | 5 | | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 9 / 60 (15.00%) | | |
| occurrences (all) | 9 | | |
| Glossodynia | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | | |
| occurrences (all) | 2 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences (all) | 3 | | |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 6 / 60 (10.00%) | | |
| occurrences (all) | 6 | | |
| Nausea | | | |
| subjects affected / exposed | 39 / 60 (65.00%) | | |
| occurrences (all) | 39 | | |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | | |
| occurrences (all) | 5 | | |
| Stomatitis | | | |
| subjects affected / exposed | 17 / 60 (28.33%) | | |
| occurrences (all) | 17 | | |
| Toothache | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences (all) | 4 | | |
| Vomiting | | | |
| subjects affected / exposed | 30 / 60 (50.00%) | | |
| occurrences (all) | 30 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|------------------|--|--|
| Alopecia | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | | |
| occurrences (all) | 8 | | |
| Dry skin | | | |
| subjects affected / exposed | 7 / 60 (11.67%) | | |
| occurrences (all) | 7 | | |
| Hair colour changes | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | | |
| occurrences (all) | 8 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences (all) | 3 | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 20 / 60 (33.33%) | | |
| occurrences (all) | 20 | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences (all) | 3 | | |
| Rash | | | |
| subjects affected / exposed | 12 / 60 (20.00%) | | |
| occurrences (all) | 12 | | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences (all) | 4 | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Micturition urgency | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Proteinuria | | | |

| | | | |
|--|---|--|--|
| <p>subjects affected / exposed occurrences (all)</p> <p>renal failure acute subjects affected / exposed occurrences (all)</p> <p>Urinary incontinence subjects affected / exposed occurrences (all)</p> | <p>0 / 60 (0.00%) 0</p> <p>1 / 60 (1.67%) 1</p> <p>0 / 60 (0.00%) 0</p> | | |
| <p>Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)</p> | <p>15 / 60 (25.00%) 15</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia subjects affected / exposed occurrences (all)</p> <p>Back pain subjects affected / exposed occurrences (all)</p> <p>Bone pain subjects affected / exposed occurrences (all)</p> <p>Flank pain subjects affected / exposed occurrences (all)</p> <p>Groin pain subjects affected / exposed occurrences (all)</p> <p>Muscle spasms subjects affected / exposed occurrences (all)</p> <p>Muscular weakness subjects affected / exposed occurrences (all)</p> <p>Musculoskeletal chest pain</p> | <p>5 / 60 (8.33%) 5</p> <p>10 / 60 (16.67%) 10</p> <p>1 / 60 (1.67%) 1</p> <p>0 / 60 (0.00%) 0</p> <p>2 / 60 (3.33%) 2</p> <p>13 / 60 (21.67%) 13</p> <p>0 / 60 (0.00%) 0</p> | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | | |
| Myalgia subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 4 | | |
| Neck pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 9 / 60 (15.00%) 9 | | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 5 / 60 (8.33%) 5 | | |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 11 / 60 (18.33%) 11 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 31 / 60 (51.67%) 31 | | |
| Dehydration subjects affected / exposed occurrences (all) | 9 / 60 (15.00%) 9 | | |
| Hyperglycaemia | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 10 / 60 (16.67%) | | |
| occurrences (all) | 10 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 7 / 60 (11.67%) | | |
| occurrences (all) | 7 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | | |
| occurrences (all) | 5 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 9 / 60 (15.00%) | | |
| occurrences (all) | 9 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 12 / 60 (20.00%) | | |
| occurrences (all) | 12 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | | |
| occurrences (all) | 4 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | | |
| occurrences (all) | 5 | | |
| Malnutrition | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences (all) | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 22 October 2010 | Suspended randomization stage and specified that all randomized subjects would undergo unblinding. Added new non-randomized cohorts ("NRE") for prostate cancer and ovarian cancer, with specific inclusion/exclusion criteria and endpoints. Updates to safety management guidelines. |
| 22 August 2011 | A second non-randomized cohort at a lower dose was added for prostate cancer. Inclusion/exclusion criteria for the non-randomized cohorts (prostate cancer and ovarian cancer) were revised. Updated safety management guidelines, including potential drug interactions. Added clarifications on dose modifications. |
| 13 August 2012 | Decreased some study procedures for subjects on study longer than 12 months. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28426123>

<http://www.ncbi.nlm.nih.gov/pubmed/30528315>

<http://www.ncbi.nlm.nih.gov/pubmed/27714541>

<http://www.ncbi.nlm.nih.gov/pubmed/23169517>

<http://www.ncbi.nlm.nih.gov/pubmed/29059635>

<http://www.ncbi.nlm.nih.gov/pubmed/28755607>

<http://www.ncbi.nlm.nih.gov/pubmed/28103611>

<http://www.ncbi.nlm.nih.gov/pubmed/24631409>

<http://www.ncbi.nlm.nih.gov/pubmed/25225437>