

**Clinical trial results:****Efficacy and Safety Study of Darolutamide (ODM-201) in Men With High-risk Non-metastatic Castration-resistant Prostate Cancer (ARAMIS)****Summary**

| | |
|--------------------------|---|
| EudraCT number | 2013-003820-36 |
| Trial protocol | SE HU FI LV CZ AT GB SK DE PT IT BE BG FR PL RO LT EE |
| Global end of trial date | 14 June 2021 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 18 June 2022 |
| First version publication date | 18 June 2022 |

Trial information**Trial identification**

| | |
|-----------------------|-------|
| Sponsor protocol code | 17712 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02200614 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 June 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 June 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the superiority of darolutamide vs. placebo in metastasis-free survival (MFS), in patients with high-risk nmCRPC.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed the informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Androgen deprivation therapy (ADT)

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 12 September 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Argentina: 5 |
| Country: Number of subjects enrolled | Australia: 21 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Belarus: 31 |
| Country: Number of subjects enrolled | Belgium: 15 |
| Country: Number of subjects enrolled | Brazil: 100 |
| Country: Number of subjects enrolled | Bulgaria: 2 |
| Country: Number of subjects enrolled | Canada: 45 |
| Country: Number of subjects enrolled | Colombia: 7 |
| Country: Number of subjects enrolled | Czechia: 29 |
| Country: Number of subjects enrolled | Estonia: 5 |
| Country: Number of subjects enrolled | Finland: 45 |
| Country: Number of subjects enrolled | France: 80 |
| Country: Number of subjects enrolled | Germany: 62 |
| Country: Number of subjects enrolled | Hungary: 28 |
| Country: Number of subjects enrolled | Israel: 1 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Italy: 30 |
| Country: Number of subjects enrolled | Japan: 95 |
| Country: Number of subjects enrolled | Korea, Republic of: 76 |
| Country: Number of subjects enrolled | Latvia: 62 |
| Country: Number of subjects enrolled | Lithuania: 79 |
| Country: Number of subjects enrolled | Peru: 22 |
| Country: Number of subjects enrolled | Poland: 33 |
| Country: Number of subjects enrolled | Portugal: 36 |
| Country: Number of subjects enrolled | Romania: 28 |
| Country: Number of subjects enrolled | Russian Federation: 105 |
| Country: Number of subjects enrolled | Serbia: 8 |
| Country: Number of subjects enrolled | Slovakia: 13 |
| Country: Number of subjects enrolled | South Africa: 16 |
| Country: Number of subjects enrolled | Spain: 117 |
| Country: Number of subjects enrolled | Sweden: 22 |
| Country: Number of subjects enrolled | Taiwan: 15 |
| Country: Number of subjects enrolled | Turkey: 27 |
| Country: Number of subjects enrolled | Ukraine: 56 |
| Country: Number of subjects enrolled | United Kingdom: 48 |
| Country: Number of subjects enrolled | United States: 139 |
| Worldwide total number of subjects | 1509 |
| EEA total number of subjects | 692 |

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) | 197 |
| From 65 to 84 years | 1182 |
| 85 years and over | 130 |

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 36 countries between 12 September 2014 (first subject first visit) and 14 June 2021 (last subject last visit).

Pre-assignment

Screening details:

From 2696 subjects who signed informed consent, 1187 subjects were discontinued from screening. A total of 1509 subjects were randomly assigned to either darolutamide arm or placebo arm. The study was unblinded on 30 OCT 2018 and subjects in the placebo arm could cross over to open-label darolutamide treatment.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Double blind treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Darolutamide (BAY1841788) |

Arm description:

Subjects received Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]).

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Darolutamide |
| Investigational medicinal product code | BAY1841788 |
| Other name | ODM-201 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

600 mg (2 tablets of 300 mg) b.i.d. with food, equal to a total daily dose of 1200 mg

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]).

| | |
|--|--------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2 tablets twice daily with food

| Number of subjects in period 1 | Darolutamide (BAY1841788) | Placebo |
|--------------------------------|---------------------------|---------|
| Started | 955 | 554 |
| Completed | 591 | 170 |
| Not completed | 364 | 384 |
| Confirmed metastasis | 120 | 140 |
| Personal reason | 77 | 85 |
| Judgment of the investigator | 59 | 99 |
| Protocol deviation | 14 | 7 |
| Adverse event | 86 | 48 |
| Other reason | 6 | 2 |
| Metastasis by local reading | 1 | 3 |
| Not treated | 1 | - |

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Open label |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Darolutamide (BAY1841788) |

Arm description:

Subjects received Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]).

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Darolutamide |
| Investigational medicinal product code | BAY1841788 |
| Other name | ODM-201 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

600 mg (2 tablets of 300 mg) b.i.d. with food, equal to a total daily dose of 1200 mg

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]).

| | |
|--|--------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

| Number of subjects in period 2 | Darolutamide (BAY1841788) | Placebo |
|---------------------------------------|------------------------------|---------|
| Started | 591 | 170 |
| Completed | 295 | 114 |
| Not completed | 296 | 56 |
| Confirmed metastasis | 1 | - |
| Personal reason | 60 | 8 |
| Judgment of the investigator | 29 | 2 |
| Protocol deviation | 3 | 2 |
| Adverse event | 41 | 11 |
| Other reason | 22 | 4 |
| Metastasis by local reading | 138 | 27 |
| Missing | 2 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Darolutamide (BAY1841788) |
|-----------------------|---------------------------|

Reporting group description:

Subjects received Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]).

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]).

| Reporting group values | Darolutamide (BAY1841788) | Placebo | Total |
|------------------------------------|------------------------------|---------|-------|
| Number of subjects | 955 | 554 | 1509 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------------|---------------|------|
| Age Continuous Units: years arithmetic mean standard deviation | 73.9 ± 7.8 | 73.2 ± 8.2 | - |
| Sex: Female, Male Units: participants | | | |
| Female | 0 | 0 | 0 |
| Male | 955 | 554 | 1509 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asia | 122 | 71 | 193 |
| Black or African American | 28 | 24 | 52 |
| White | 760 | 434 | 1194 |
| Missing | 36 | 19 | 55 |
| Other | 9 | 6 | 15 |

End points

End points reporting groups

| | |
|---|---------------------------|
| Reporting group title | Darolutamide (BAY1841788) |
| Reporting group description: Subjects received Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]). | |
| Reporting group title | Placebo |
| Reporting group description: Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]). | |
| Reporting group title | Darolutamide (BAY1841788) |
| Reporting group description: Subjects received Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]). | |
| Reporting group title | Placebo |
| Reporting group description: Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]). | |

Primary: Metastasis-Free Survival

| | |
|---|--------------------------|
| End point title | Metastasis-Free Survival |
| End point description: Metastasis-Free Survival (MFS) is defined as the time from randomisation to evidence of metastasis or death from any cause, whichever occurs first (cut-off date 15 Nov 2019). 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events. | |
| End point type | Primary |
| End point timeframe: From randomization to the time approximately 385 MFS events were observed (approximately 48 months) | |

| End point values | Darolutamide (BAY1841788) | Placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 955 | 554 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 40.37 (34.33 to 99999) | 18.43 (15.51 to 22.34) | | |

Statistical analyses

| | |
|----------------------------|-------------------------------------|
| Statistical analysis title | Metastasis-Free Survival |
| Comparison groups | Darolutamide (BAY1841788) v Placebo |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.000001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.413 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.341 |
| upper limit | 0.5 |

Notes:

[1] - Hazard ratio and 95% Confidence Interval (CI) was based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Overall Survival - Primary analysis

| | |
|--|-------------------------------------|
| End point title | Overall Survival - Primary analysis |
| End point description: | |
| Overall Survival (OS) was defined as the time from randomization to death due to any cause. 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization of the first subject to the time approximatively 140 death events were observed (approximately 48 months) | |

| End point values | Darolutamide (BAY1841788) | Placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 955 | 554 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (44.45 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Overall Survival |
| Statistical analysis description: | |
| Primary analysis | |
| Comparison groups | Darolutamide (BAY1841788) v Placebo |
| Number of subjects included in analysis | 1509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.04521 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.706 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.501 |
| upper limit | 0.994 |

Notes:

[2] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to pain progression - Primary analysis

| | |
|-----------------|---|
| End point title | Time to pain progression - Primary analysis |
|-----------------|---|

End point description:

Time to pain progression (PP) is defined as time from randomization to pain progression, where progression is defined as an increase of 2 or more points from baseline in question 3 of the Brief Pain Inventory-Short Form questionnaire (BPI-SF) related to the worst pain in the last 24 hours taken as a 7-day average for post-baseline scores, or initiation of short or long-acting opioids for pain, whichever comes first. Initiation or change in the use of other non-opioid analgesics is not used in the analysis of pain progression.

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

End point timeframe:

From randomization until last study treatment (assessed every 4 months) (approximately 48 months)

| End point values | Darolutamide (BAY1841788) | Placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 955 | 554 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 40.31 (33.21 to 41.20) | 25.36 (19.09 to 29.63) | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Time to pain progression |
|----------------------------|--------------------------|

Statistical analysis description:

Primary analysis

| | |
|---|-------------------------------------|
| Comparison groups | Darolutamide (BAY1841788) v Placebo |
| Number of subjects included in analysis | 1509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.000008 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.647 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.533 |
| upper limit | 0.785 |

Notes:

[3] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to initiation of first cytotoxic chemotherapy for prostate cancer - Primary analysis

| | |
|-----------------|---|
| End point title | Time to initiation of first cytotoxic chemotherapy for prostate cancer - Primary analysis |
|-----------------|---|

End point description:

The time to cytotoxic chemotherapy was defined as the time from randomization to the start of the first cytotoxic chemotherapy cycle. 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events.

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

End point timeframe:

From randomization until last study treatment (assessed every 4 months) (approximately 48 months)

| | | | | |
|----------------------------------|---------------------------|------------------------|--|--|
| End point values | Darolutamide (BAY1841788) | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 955 | 554 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 38.21 (35.55 to 41.89) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Time to initiation of first cytotoxic chemotherapy |
|-----------------------------------|--|

Statistical analysis description:

Primary analysis

| | |
|---|-------------------------------------|
| Comparison groups | Darolutamide (BAY1841788) v Placebo |
| Number of subjects included in analysis | 1509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | < 0.000001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.433 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.314 |
| upper limit | 0.595 |

Notes:

[4] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to first symptomatic skeletal event (SSE) - Primary analysis

| | |
|-----------------|--|
| End point title | Time to first symptomatic skeletal event (SSE) - Primary |
|-----------------|--|

End point description:

The time to the first SSE was defined as the time from randomization to the occurrence of the first SSE. 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events.

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

End point timeframe:

From randomization until last study treatment (assessed every 4 months) (approximately 48 months)

| End point values | Darolutamide (BAY1841788) | Placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 955 | 554 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

| | |
|----------------------------|-------------------|
| Statistical analysis title | Time to first SSE |
|----------------------------|-------------------|

Statistical analysis description:

Primary analysis

| | |
|---|-------------------------------------|
| Comparison groups | Darolutamide (BAY1841788) v Placebo |
| Number of subjects included in analysis | 1509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.011262 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.428 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.218 |
| upper limit | 0.842 |

Notes:

[5] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Overall Survival - Final analysis

| | |
|-----------------|-----------------------------------|
| End point title | Overall Survival - Final analysis |
|-----------------|-----------------------------------|

End point description:

Overall Survival (OS) was defined as the time from randomization to death due to any cause. The final analysis was done at the time of the data cut-off (15 NOV 2019). 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events.

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

End point timeframe:

From randomization of the first subject to the time approximately 254 death events were observed (approximately 56 months)

| End point values | Darolutamide (BAY1841788) | Placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 955 | 554 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (56.14 to 99999) | 99999 (46.91 to 99999) | | |

Statistical analyses

| Statistical analysis title | Overall Survival |
|---|-------------------------------------|
| Statistical analysis description: | |
| Final analysis | |
| Comparison groups | Darolutamide (BAY1841788) v Placebo |
| Number of subjects included in analysis | 1509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| P-value | = 0.003048 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.685 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.533 |
| upper limit | 0.881 |

Notes:

[6] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to pain progression - Final analysis

| End point title | Time to pain progression - Final analysis |
|---|---|
| End point description: | |
| For time to pain progression, the analysis performed using the primary completion cut-off data (03 SEP 2018) was considered final and no new analysis was performed for time to pain progression. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until last study treatment (assessed every 4 months) (approximately 48 months) | |

| End point values | Darolutamide (BAY1841788) | Placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 955 | 554 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 40.31 (33.21 to 41.20) | 25.36 (19.09 to 29.63) | | |

Statistical analyses

| Statistical analysis title | Time to pain progression |
|---|-------------------------------------|
| Statistical analysis description: | |
| Final analysis | |
| Comparison groups | Darolutamide (BAY1841788) v Placebo |
| Number of subjects included in analysis | 1509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | = 0.000008 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.647 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.533 |
| upper limit | 0.785 |

Notes:

[7] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to initiation of first cytotoxic chemotherapy for prostate cancer - Final analysis

| End point title | Time to initiation of first cytotoxic chemotherapy for prostate cancer - Final analysis |
|---|---|
| End point description: | |
| The time to cytotoxic chemotherapy was defined as the time from randomization to the start of the first cytotoxic chemotherapy cycle. The final analysis was done at the time of the data cut-off (15 NOV 2019). 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until initiation of first cytotoxic chemotherapy treatment (approximately 59 months) | |

| End point values | Darolutamide (BAY1841788) | Placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 955 | 554 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

| Statistical analysis title | Time to initiation of first cytotoxic chemotherapy |
|---|--|
| Statistical analysis description: | |
| Final analysis | |
| Comparison groups | Darolutamide (BAY1841788) v Placebo |
| Number of subjects included in analysis | 1509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| P-value | = 0.000044 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.579 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.444 |
| upper limit | 0.755 |

Notes:

[8] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Secondary: Time to first symptomatic skeletal event (SSE) - Final analysis

| End point title | Time to first symptomatic skeletal event (SSE) - Final analysis |
|--|---|
| End point description: | |
| The time to the first SSE was defined as the time from randomization to the occurrence of the first SSE. The final analysis was done at the time of the data cut-off (15 NOV 2019). 99999 = value cannot be estimated due to censored data, insufficient number of subjects with events. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until occurrence of first SSE event (approximately 59 months) | |

| End point values | Darolutamide (BAY1841788) | Placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 955 | 554 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Time to first SSE |
| Statistical analysis description: | |
| Final analysis | |
| Comparison groups | Darolutamide (BAY1841788) v Placebo |
| Number of subjects included in analysis | 1509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | = 0.005294 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.484 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.287 |
| upper limit | 0.815 |

Notes:

[9] - The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by Prostate-specific antigen doubling time (PSADT) (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (No, Yes).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration until 30 days after last treatment (last cut-off date 14 JUN 2021)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Darolutamide (DB) |
|-----------------------|-------------------|

Reporting group description:

Subjects received darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg (double blind [DB]).

| | |
|-----------------------|---------------------------|
| Reporting group title | Placebo+Darolutamide (CO) |
|-----------------------|---------------------------|

Reporting group description:

Subjects received matching placebo 2 tablets twice daily with food. Subjects from the placebo arm crossed over to receive open-label darolutamide treatment (placebo-darolutamide cross-over [CO]).

| | |
|-----------------------|--------------|
| Reporting group title | Placebo (DB) |
|-----------------------|--------------|

Reporting group description:

Subjects received matching placebo 2 tablets twice daily with food (double blind [DB]).

| | |
|-----------------------|----------------------|
| Reporting group title | Darolutamide (DB+OL) |
|-----------------------|----------------------|

Reporting group description:

Subjects received darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Subjects in the darolutamide treatment arm were ongoing with open-label darolutamide treatment (darolutamide double-blind [DB] + open-label [OL]).

| Serious adverse events | Darolutamide (DB) | Placebo+Darolutamide (CO) | Placebo (DB) |
|---|--------------------|---------------------------|--------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 251 / 954 (26.31%) | 43 / 170 (25.29%) | 121 / 554 (21.84%) |
| number of deaths (all causes) | 155 | 16 | 137 |
| number of deaths resulting from adverse events | 38 | 6 | 19 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute leukaemia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Benign hepatic neoplasm | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder neoplasm | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 1 / 170 (0.59%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Carcinoid tumour | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Choroid melanoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Colon cancer | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Gastric cancer | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 2 / 554 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngeal cancer | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipoma | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Lymphoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 melanoma in situ | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Meningioma | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mesothelioma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Metastases to spine | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasm malignant | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pituitary tumour | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 adenocarcinoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 cancer | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Thymoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 stromal tumour | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Colorectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma pancreas | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine carcinoma | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Lung neoplasm malignant | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Brain neoplasm | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon neoplasm | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Salivary gland neoplasm | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 neoplasm | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 neoplasm | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine tumour of the lung | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Aortic stenosis | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Aortic thrombosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Hypotension | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Iliac artery stenosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Embolism | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Angioplasty | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder catheterisation | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Hip arthroplasty | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia repair | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Orchidectomy | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transurethral prostatectomy | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrostomy | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary angioplasty | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Artificial urinary sphincter implant | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiotherapy to brain | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatectomy | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary resection | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Chest pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Death | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Sudden death | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| General physical health deterioration | | | |
| subjects affected / exposed | 5 / 954 (0.52%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatic obstruction | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate induration | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Perineal pain | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| 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 | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 3 / 554 (0.54%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 3 / 554 (0.54%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | 0 / 170 (0.00%) | 2 / 554 (0.36%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Epistaxis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Pulmonary artery thrombosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 5 / 954 (0.52%) | 1 / 170 (0.59%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary mass | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Major depression | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Biopsy prostate | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Body temperature increased | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Prostatic specific antigen increased | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Urine output decreased | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Angiogram | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 2 / 554 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Bite | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incisional hernia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Multiple injuries | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 proctitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Stenosis of vesicourethral anastomosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Contusion | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Thermal burn | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Postoperative ileus | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Vascular procedure complication | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Heart injury | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Skull fracture | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Vascular graft complication | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Flatback syndrome | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Incarcerated parastomal hernia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Pyloric stenosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| 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 | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 5 / 954 (0.52%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | 1 / 170 (0.59%) | 2 / 554 (0.36%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Arrhythmia | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 8 / 954 (0.84%) | 3 / 170 (1.76%) | 3 / 554 (0.54%) |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Atrioventricular block | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Bradycardia | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 3 / 554 (0.54%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| Cardiac failure | | | |
| subjects affected / exposed | 8 / 954 (0.84%) | 2 / 170 (1.18%) | 4 / 554 (0.72%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 2 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 3 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Conduction disorder | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Coronary artery disease | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Hypertensive heart disease | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Myocardial infarction | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | 2 / 170 (1.18%) | 2 / 554 (0.36%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| 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 disorder | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Aortic valve disease | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Nervous system disorders | | | |
| Autonomic nervous system imbalance | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bulbar palsy | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Cerebral infarction | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cerebrovascular accident | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 954 (0.21%) | 1 / 170 (0.59%) | 3 / 554 (0.54%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelopathy | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Normal pressure hydrocephalus | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Seizure | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Subarachnoid haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 2 / 554 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Perineurial cyst | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| IIIrd nerve disorder | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 5 / 954 (0.52%) | 1 / 170 (0.59%) | 2 / 554 (0.36%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Partial seizures | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Parkinson's disease | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertebrobasilar stroke | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 1 / 170 (0.59%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune haemolytic anaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Immune thrombocytopenia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Device dislocation | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device occlusion | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal detachment | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal vascular disorder | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Macular hole | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal mass | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| 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 | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Constipation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| 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 pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 / 954 (0.10%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Intestinal infarction | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 954 (0.42%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Melaena | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic cyst | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 acute | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plicated tongue | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Proctitis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 haemorrhage | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Rectal stenosis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Small intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 2 / 554 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal perforation | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 haemorrhage | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterovesical fistula | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Bowel movement irregularity | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Hiatus hernia, obstructive | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstructive pancreatitis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 1 / 170 (0.59%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 function abnormal | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Liver disorder | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Bile duct stenosis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Biliary obstruction | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin mass | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Azotaemia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Calculus bladder | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Dysuria | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 3 / 554 (0.54%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 11 / 954 (1.15%) | 0 / 170 (0.00%) | 7 / 554 (1.26%) |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 0 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 2 / 170 (1.18%) | 4 / 554 (0.72%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Oliguria | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 4 / 554 (0.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Ureteric stenosis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 retention | | | |

| | | | |
|---|------------------|-----------------|------------------|
| subjects affected / exposed | 16 / 954 (1.68%) | 6 / 170 (3.53%) | 20 / 554 (3.61%) |
| occurrences causally related to treatment / all | 1 / 17 | 0 / 6 | 1 / 20 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract disorder | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urine flow decreased | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 7 / 954 (0.73%) | 1 / 170 (0.59%) | 3 / 554 (0.54%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 2 / 554 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethral stenosis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | 1 / 170 (0.59%) | 3 / 554 (0.54%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower urinary tract symptoms | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Bladder outlet obstruction | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Back pain | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Flank pain | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Kyphosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 osteoarthritis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Rapidly progressive osteoarthritis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal stenosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 | | | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis gangrenous | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Erysipelas | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Hepatitis C | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 2 / 554 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Meningitis bacterial | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perinephric abscess | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 15 / 954 (1.57%) | 1 / 170 (0.59%) | 6 / 554 (1.08%) |
| occurrences causally related to treatment / all | 0 / 18 | 0 / 2 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sialoadenitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Tick-borne viral encephalitis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 954 (0.73%) | 1 / 170 (0.59%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vestibular neuronitis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Urosepsis | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 1 / 170 (0.59%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute endocarditis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 infection bacterial | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| 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 sepsis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Wound abscess | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Klebsiella bacteraemia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral discitis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 abscess | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Severe acute respiratory syndrome | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Medical device site infection | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (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 |
| Varicella zoster virus infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Medical device site joint infection | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 1 / 170 (0.59%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Diverticulitis intestinal perforated | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suspected COVID-19 | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | 0 / 170 (0.00%) | 0 / 554 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Dehydration | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Diabetes mellitus | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | 0 / 170 (0.00%) | 1 / 554 (0.18%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | 0 / 170 (0.00%) | 0 / 554 (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 |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | 0 / 170 (0.00%) | 0 / 554 (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 |

| Serious adverse events | Darolutamide (DB+OL) | | |
|---|----------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 367 / 954 (38.47%) | | |
| number of deaths (all causes) | 224 | | |
| number of deaths resulting from adverse events | 63 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute leukaemia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Benign hepatic neoplasm | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bladder cancer | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bladder neoplasm | | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bladder transitional cell carcinoma | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Carcinoid tumour | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Choroid melanoma | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colon cancer | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diffuse large B-cell lymphoma | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric cancer | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngeal cancer | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lipoma | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung adenocarcinoma | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lymphoma | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malignant melanoma in situ | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meningioma | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mesothelioma | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastases to spine | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasm malignant | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pituitary tumour | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal cancer | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thymoma | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transitional cell carcinoma | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tumour pain | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal stromal tumour | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colorectal adenocarcinoma | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Adenocarcinoma pancreas | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuroendocrine carcinoma | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung neoplasm malignant | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prostate cancer | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Brain neoplasm | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colon neoplasm | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Salivary gland neoplasm | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung neoplasm | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal neoplasm | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatocellular carcinoma | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuroendocrine tumour of the lung | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic thrombosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lymphoedema | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Orthostatic hypotension | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral ischaemia | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thrombosis | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Venous thrombosis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subclavian vein thrombosis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Deep vein thrombosis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Iliac artery stenosis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Angioplasty | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder catheterisation | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia repair | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orchidectomy | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transurethral prostatectomy | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrostomy | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary angioplasty | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Artificial urinary sphincter implant | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radiotherapy to brain | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostatectomy | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary resection | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 6 / 954 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 6 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 7 / 954 (0.73%) | | |
| occurrences causally related to treatment / all | 0 / 11 | | |
| deaths causally related to treatment / all | 0 / 4 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |

| | | | | |
|---|-----------------|--|--|--|
| Benign prostatic hyperplasia | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prostatic obstruction | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prostate induration | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Perineal pain | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| 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 | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cough | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 5 / 954 (0.52%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |

| | | | | |
|---|-----------------|--|--|--|
| Epistaxis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia aspiration | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary artery thrombosis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary embolism | | | | |
| subjects affected / exposed | 7 / 954 (0.73%) | | | |
| occurrences causally related to treatment / all | 1 / 7 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Pulmonary thrombosis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory distress | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory failure | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary mass | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Major depression | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Biopsy prostate | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Blood creatinine increased subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Body temperature increased subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostatic specific antigen increased subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transaminases increased subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urine output decreased subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angiocardiogram subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Ankle fracture subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Bite | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Facial bones fracture | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fall | | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femoral neck fracture | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femur fracture | | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fibula fracture | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Foot fracture | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fracture | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hand fracture | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Head injury | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Hip fracture | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Humerus fracture | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Incisional hernia | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ligament sprain | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple injuries | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Patella fracture | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Radiation proctitis | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Radius fracture | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rib fracture | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Road traffic accident | | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Subdural haematoma | | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tibia fracture | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ulna fracture | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Wrist fracture | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Stenosis of vesicourethral anastomosis | | | | |

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|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Contusion | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thermal burn | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Postoperative ileus | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vascular procedure complication | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Heart injury | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Skull fracture | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vascular graft complication | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Flatback syndrome | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Incarcerated parastomal hernia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Pyloric stenosis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 6 / 954 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Arrhythmia | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arteriosclerosis coronary artery | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 9 / 954 (0.94%) | | | |
| occurrences causally related to treatment / all | 0 / 12 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial flutter | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrioventricular block | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrioventricular block complete | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrioventricular block second degree | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bradycardia | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 12 / 954 (1.26%) | | |
| occurrences causally related to treatment / all | 0 / 14 | | |
| deaths causally related to treatment / all | 0 / 7 | | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Conduction disorder | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive heart disease | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial infarction | | | | |
| subjects affected / exposed | 11 / 954 (1.15%) | | | |
| occurrences causally related to treatment / all | 0 / 12 | | | |
| deaths causally related to treatment / all | 0 / 3 | | | |
| Myocardial ischaemia | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Palpitations | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sinus bradycardia | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tachycardia | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute coronary syndrome | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorder | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Aortic valve disease | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Autonomic nervous system imbalance | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bulbar palsy | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 6 / 954 (0.63%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dizziness | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhage intracranial | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhagic stroke | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myelopathy | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Normal pressure hydrocephalus | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Presyncope | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seizure | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subarachnoid haemorrhage | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Syncope | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transient ischaemic attack | | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Brain oedema | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Perineurial cyst | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| IIIrd nerve disorder | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cognitive disorder | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ischaemic stroke | | | | |
| subjects affected / exposed | 5 / 954 (0.52%) | | | |
| occurrences causally related to treatment / all | 1 / 6 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Partial seizures | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Parkinson's disease | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertebrobasilar stroke | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 954 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune haemolytic anaemia | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune thrombocytopenia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device dislocation | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device occlusion | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal detachment | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal vascular disorder | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Macular hole | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal mass | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Enterocolitis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric haemorrhage | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastritis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal disorder | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal necrosis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal pain | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhoids | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hiatus hernia | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ileus | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Incarcerated inguinal hernia | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Inguinal hernia | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal infarction | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Intestinal ischaemia | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Intestinal obstruction | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 4 / 954 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Melaena | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatic cyst | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis acute | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Plicated tongue | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Proctitis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal haemorrhage | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal stenosis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal perforation | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Umbilical hernia | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumoperitoneum | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anal haemorrhage | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subileus | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestine polyp | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterovesical fistula | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bowel movement irregularity | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hiatus hernia, obstructive | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstructive pancreatitis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis acute | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Liver disorder | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Biliary obstruction | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin mass | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Azotaemia | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Calculus bladder | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Calculus urinary | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 25 / 954 (2.62%) | | |
| occurrences causally related to treatment / all | 0 / 29 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 8 / 954 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephritis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nephrolithiasis | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oliguria | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pollakiuria | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal colic | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal failure | | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Ureteric obstruction | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ureteric stenosis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary retention | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 33 / 954 (3.46%) | | |
| occurrences causally related to treatment / all | 1 / 37 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract disorder | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urine flow decreased | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 11 / 954 (1.15%) | | |
| occurrences causally related to treatment / all | 0 / 13 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urethral stenosis | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 7 / 954 (0.73%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower urinary tract symptoms | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder outlet obstruction | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Kyphosis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 4 / 954 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pain in extremity | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rheumatoid arthritis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rotator cuff syndrome | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal osteoarthritis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral disc protrusion | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal pain | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rapidly progressive osteoarthritis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal stenosis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis gangrenous | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dengue fever | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Erysipelas | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatitis C | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infectious mononucleosis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Meningitis bacterial | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Osteomyelitis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Perinephric abscess | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 20 / 954 (2.10%) | | | |
| occurrences causally related to treatment / all | 0 / 24 | | | |
| deaths causally related to treatment / all | 0 / 3 | | | |
| Pneumonia pneumococcal | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia staphylococcal | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary tuberculosis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis acute | | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sialoadenitis | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Tick-borne viral encephalitis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 12 / 954 (1.26%) | | | |
| occurrences causally related to treatment / all | 0 / 13 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vestibular neuronitis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Wound infection | | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urosepsis | | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 10 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute endocarditis | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection bacterial | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infective exacerbation of chronic obstructive airways disease | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal sepsis | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Wound abscess | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Klebsiella bacteraemia | | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral discitis | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal abscess | | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacterial infection | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Severe acute respiratory syndrome | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis infective | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Medical device site infection | | | |
| subjects affected / exposed | 0 / 954 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Varicella zoster virus infection | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Medical device site joint infection | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COVID-19 | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Diverticulitis intestinal perforated | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Suspected COVID-19 | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 954 (0.21%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 954 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 954 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 954 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Darolutamide (DB) | Placebo+Darolutamide (CO) | Placebo (DB) |
|---|--------------------|---------------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 673 / 954 (70.55%) | 110 / 170 (64.71%) | 354 / 554 (63.90%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 66 / 954 (6.92%) | 6 / 170 (3.53%) | 31 / 554 (5.60%) |
| occurrences (all) | 86 | 7 | 39 |
| Hot flush | | | |
| subjects affected / exposed | 54 / 954 (5.66%) | 3 / 170 (1.76%) | 25 / 554 (4.51%) |
| occurrences (all) | 58 | 3 | 25 |
| General disorders and administration site conditions | | | |

| | | | |
|---|--------------------|-----------------|------------------|
| Asthenia | | | |
| subjects affected / exposed | 37 / 954 (3.88%) | 7 / 170 (4.12%) | 20 / 554 (3.61%) |
| occurrences (all) | 42 | 8 | 23 |
| Fatigue | | | |
| subjects affected / exposed | 126 / 954 (13.21%) | 9 / 170 (5.29%) | 47 / 554 (8.48%) |
| occurrences (all) | 164 | 9 | 60 |
| Oedema peripheral | | | |
| subjects affected / exposed | 43 / 954 (4.51%) | 4 / 170 (2.35%) | 17 / 554 (3.07%) |
| occurrences (all) | 49 | 4 | 19 |
| Pyrexia | | | |
| subjects affected / exposed | 18 / 954 (1.89%) | 5 / 170 (2.94%) | 5 / 554 (0.90%) |
| occurrences (all) | 25 | 9 | 7 |
| Reproductive system and breast disorders | | | |
| Gynaecomastia | | | |
| subjects affected / exposed | 21 / 954 (2.20%) | 1 / 170 (0.59%) | 6 / 554 (1.08%) |
| occurrences (all) | 21 | 1 | 6 |
| Pelvic pain | | | |
| subjects affected / exposed | 13 / 954 (1.36%) | 1 / 170 (0.59%) | 12 / 554 (2.17%) |
| occurrences (all) | 15 | 1 | 13 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 29 / 954 (3.04%) | 6 / 170 (3.53%) | 11 / 554 (1.99%) |
| occurrences (all) | 34 | 6 | 11 |
| Dyspnoea | | | |
| subjects affected / exposed | 26 / 954 (2.73%) | 2 / 170 (1.18%) | 16 / 554 (2.89%) |
| occurrences (all) | 28 | 3 | 22 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 26 / 954 (2.73%) | 8 / 170 (4.71%) | 11 / 554 (1.99%) |
| occurrences (all) | 28 | 8 | 11 |
| Depression | | | |
| subjects affected / exposed | 20 / 954 (2.10%) | 2 / 170 (1.18%) | 9 / 554 (1.62%) |
| occurrences (all) | 20 | 2 | 10 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |

| | | | |
|---|------------------------|-----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 6 / 954 (0.63%) 8 | 6 / 170 (3.53%) 9 | 1 / 554 (0.18%) 1 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 12 / 954 (1.26%) 16 | 6 / 170 (3.53%) 10 | 1 / 554 (0.18%) 1 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 23 / 954 (2.41%) 32 | 3 / 170 (1.76%) 3 | 14 / 554 (2.53%) 19 |
| Weight decreased subjects affected / exposed occurrences (all) | 40 / 954 (4.19%) 42 | 8 / 170 (4.71%) 8 | 14 / 554 (2.53%) 17 |
| Weight increased subjects affected / exposed occurrences (all) | 14 / 954 (1.47%) 15 | 3 / 170 (1.76%) 3 | 7 / 554 (1.26%) 8 |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 41 / 954 (4.30%) 44 | 7 / 170 (4.12%) 8 | 23 / 554 (4.15%) 27 |
| Rib fracture subjects affected / exposed occurrences (all) | 16 / 954 (1.68%) 17 | 6 / 170 (3.53%) 6 | 8 / 554 (1.44%) 10 |
| Contusion subjects affected / exposed occurrences (all) | 12 / 954 (1.26%) 17 | 2 / 170 (1.18%) 2 | 2 / 554 (0.36%) 2 |
| Cardiac disorders | | | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 19 / 954 (1.99%) 20 | 3 / 170 (1.76%) 4 | 6 / 554 (1.08%) 8 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 39 / 954 (4.09%) 47 | 2 / 170 (1.18%) 2 | 14 / 554 (2.53%) 17 |
| Headache subjects affected / exposed occurrences (all) | 41 / 954 (4.30%) 59 | 4 / 170 (2.35%) 7 | 14 / 554 (2.53%) 15 |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| Anaemia subjects affected / exposed occurrences (all) | 60 / 954 (6.29%) 76 | 7 / 170 (4.12%) 7 | 28 / 554 (5.05%) 33 |
| Neutropenia subjects affected / exposed occurrences (all) | 13 / 954 (1.36%) 17 | 2 / 170 (1.18%) 2 | 4 / 554 (0.72%) 4 |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 11 / 954 (1.15%) 11 | 4 / 170 (2.35%) 4 | 5 / 554 (0.90%) 6 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 25 / 954 (2.62%) 27 | 2 / 170 (1.18%) 2 | 12 / 554 (2.17%) 14 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 14 / 954 (1.47%) 16 | 3 / 170 (1.76%) 3 | 14 / 554 (2.53%) 15 |
| Diarrhoea subjects affected / exposed occurrences (all) | 69 / 954 (7.23%) 87 | 15 / 170 (8.82%) 16 | 33 / 554 (5.96%) 37 |
| Constipation subjects affected / exposed occurrences (all) | 65 / 954 (6.81%) 70 | 8 / 170 (4.71%) 11 | 36 / 554 (6.50%) 41 |
| Nausea subjects affected / exposed occurrences (all) | 53 / 954 (5.56%) 59 | 6 / 170 (3.53%) 6 | 32 / 554 (5.78%) 37 |
| Vomiting subjects affected / exposed occurrences (all) | 17 / 954 (1.78%) 19 | 3 / 170 (1.76%) 3 | 10 / 554 (1.81%) 12 |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 17 / 954 (1.78%) 20 | 2 / 170 (1.18%) 4 | 12 / 554 (2.17%) 14 |
| Rash subjects affected / exposed occurrences (all) | 17 / 954 (1.78%) 17 | 2 / 170 (1.18%) 2 | 4 / 554 (0.72%) 4 |
| Renal and urinary disorders | | | |

| | | | |
|---|--------------------|-------------------|-------------------|
| Dysuria | | | |
| subjects affected / exposed | 24 / 954 (2.52%) | 5 / 170 (2.94%) | 27 / 554 (4.87%) |
| occurrences (all) | 27 | 5 | 30 |
| Haematuria | | | |
| subjects affected / exposed | 37 / 954 (3.88%) | 12 / 170 (7.06%) | 27 / 554 (4.87%) |
| occurrences (all) | 48 | 13 | 39 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 14 / 954 (1.47%) | 3 / 170 (1.76%) | 4 / 554 (0.72%) |
| occurrences (all) | 17 | 3 | 4 |
| Nocturia | | | |
| subjects affected / exposed | 17 / 954 (1.78%) | 2 / 170 (1.18%) | 10 / 554 (1.81%) |
| occurrences (all) | 17 | 2 | 10 |
| Pollakiuria | | | |
| subjects affected / exposed | 41 / 954 (4.30%) | 4 / 170 (2.35%) | 18 / 554 (3.25%) |
| occurrences (all) | 46 | 4 | 20 |
| Urinary incontinence | | | |
| subjects affected / exposed | 15 / 954 (1.57%) | 3 / 170 (1.76%) | 14 / 554 (2.53%) |
| occurrences (all) | 15 | 3 | 14 |
| Urinary retention | | | |
| subjects affected / exposed | 25 / 954 (2.62%) | 1 / 170 (0.59%) | 24 / 554 (4.33%) |
| occurrences (all) | 27 | 1 | 29 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 92 / 954 (9.64%) | 9 / 170 (5.29%) | 52 / 554 (9.39%) |
| occurrences (all) | 104 | 9 | 59 |
| Arthralgia | | | |
| subjects affected / exposed | 106 / 954 (11.11%) | 17 / 170 (10.00%) | 58 / 554 (10.47%) |
| occurrences (all) | 146 | 19 | 69 |
| Muscle spasms | | | |
| subjects affected / exposed | 19 / 954 (1.99%) | 0 / 170 (0.00%) | 4 / 554 (0.72%) |
| occurrences (all) | 20 | 0 | 4 |
| Myalgia | | | |
| subjects affected / exposed | 18 / 954 (1.89%) | 2 / 170 (1.18%) | 7 / 554 (1.26%) |
| occurrences (all) | 21 | 3 | 8 |
| Osteoarthritis | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 16 / 954 (1.68%) 20 | 3 / 170 (1.76%) 3 | 3 / 554 (0.54%) 3 |
| Pain in extremity subjects affected / exposed occurrences (all) | 60 / 954 (6.29%) 79 | 5 / 170 (2.94%) 6 | 19 / 554 (3.43%) 25 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 13 / 954 (1.36%) 17 | 3 / 170 (1.76%) 3 | 9 / 554 (1.62%) 10 |
| Influenza subjects affected / exposed occurrences (all) | 28 / 954 (2.94%) 33 | 2 / 170 (1.18%) 2 | 8 / 554 (1.44%) 8 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 39 / 954 (4.09%) 50 | 8 / 170 (4.71%) 11 | 23 / 554 (4.15%) 27 |
| Pneumonia subjects affected / exposed occurrences (all) | 10 / 954 (1.05%) 11 | 3 / 170 (1.76%) 3 | 5 / 554 (0.90%) 5 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 44 / 954 (4.61%) 59 | 12 / 170 (7.06%) 12 | 31 / 554 (5.60%) 37 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 26 / 954 (2.73%) 29 | 3 / 170 (1.76%) 7 | 10 / 554 (1.81%) 13 |
| COVID-19 subjects affected / exposed occurrences (all) | 0 / 954 (0.00%) 0 | 4 / 170 (2.35%) 4 | 0 / 554 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 16 / 954 (1.68%) 24 | 0 / 170 (0.00%) 0 | 9 / 554 (1.62%) 10 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 10 / 954 (1.05%) 10 | 4 / 170 (2.35%) 4 | 2 / 554 (0.36%) 2 |
| Decreased appetite | | | |

| | | | |
|-----------------------------|------------------|-----------------|------------------|
| subjects affected / exposed | 30 / 954 (3.14%) | 1 / 170 (0.59%) | 16 / 554 (2.89%) |
| occurrences (all) | 34 | 1 | 18 |

| Non-serious adverse events | Darolutamide (DB+OL) | | |
|---|-------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 742 / 954 (77.78%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 87 / 954 (9.12%) | | |
| occurrences (all) | 117 | | |
| Hot flush | | | |
| subjects affected / exposed | 67 / 954 (7.02%) | | |
| occurrences (all) | 73 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 43 / 954 (4.51%) | | |
| occurrences (all) | 53 | | |
| Fatigue | | | |
| subjects affected / exposed | 142 / 954 (14.88%) | | |
| occurrences (all) | 198 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 57 / 954 (5.97%) | | |
| occurrences (all) | 67 | | |
| Pyrexia | | | |
| subjects affected / exposed | 21 / 954 (2.20%) | | |
| occurrences (all) | 28 | | |
| Reproductive system and breast disorders | | | |
| Gynaecomastia | | | |
| subjects affected / exposed | 30 / 954 (3.14%) | | |
| occurrences (all) | 30 | | |
| Pelvic pain | | | |
| subjects affected / exposed | 16 / 954 (1.68%) | | |
| occurrences (all) | 19 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|------------------------|--|--|
| Cough subjects affected / exposed occurrences (all) | 33 / 954 (3.46%) 38 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 32 / 954 (3.35%) 34 | | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 35 / 954 (3.67%) 38 | | |
| Depression subjects affected / exposed occurrences (all) | 25 / 954 (2.62%) 27 | | |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 13 / 954 (1.36%) 16 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 23 / 954 (2.41%) 29 | | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 37 / 954 (3.88%) 51 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 65 / 954 (6.81%) 72 | | |
| Weight increased subjects affected / exposed occurrences (all) | 25 / 954 (2.62%) 27 | | |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 62 / 954 (6.50%) 69 | | |
| Rib fracture subjects affected / exposed occurrences (all) | 28 / 954 (2.94%) 30 | | |

| | | | |
|---|---|--|--|
| Contusion subjects affected / exposed occurrences (all) | 21 / 954 (2.20%) 26 | | |
| Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) | 26 / 954 (2.73%) 30 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 48 / 954 (5.03%) 64 53 / 954 (5.56%) 75 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) | 93 / 954 (9.75%) 136 21 / 954 (2.20%) 27 | | |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 15 / 954 (1.57%) 16 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation | 35 / 954 (3.67%) 39 16 / 954 (1.68%) 19 87 / 954 (9.12%) 114 | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 84 / 954 (8.81%) | | |
| occurrences (all) | 94 | | |
| Nausea | | | |
| subjects affected / exposed | 60 / 954 (6.29%) | | |
| occurrences (all) | 76 | | |
| Vomiting | | | |
| subjects affected / exposed | 21 / 954 (2.20%) | | |
| occurrences (all) | 24 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 22 / 954 (2.31%) | | |
| occurrences (all) | 25 | | |
| Rash | | | |
| subjects affected / exposed | 24 / 954 (2.52%) | | |
| occurrences (all) | 27 | | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 32 / 954 (3.35%) | | |
| occurrences (all) | 37 | | |
| Haematuria | | | |
| subjects affected / exposed | 66 / 954 (6.92%) | | |
| occurrences (all) | 96 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 21 / 954 (2.20%) | | |
| occurrences (all) | 25 | | |
| Nocturia | | | |
| subjects affected / exposed | 23 / 954 (2.41%) | | |
| occurrences (all) | 24 | | |
| Pollakiuria | | | |
| subjects affected / exposed | 51 / 954 (5.35%) | | |
| occurrences (all) | 63 | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 24 / 954 (2.52%) | | |
| occurrences (all) | 25 | | |
| Urinary retention | | | |

| | | | |
|---|--------------------|--|--|
| subjects affected / exposed | 39 / 954 (4.09%) | | |
| occurrences (all) | 47 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 118 / 954 (12.37%) | | |
| occurrences (all) | 142 | | |
| Arthralgia | | | |
| subjects affected / exposed | 135 / 954 (14.15%) | | |
| occurrences (all) | 190 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 20 / 954 (2.10%) | | |
| occurrences (all) | 21 | | |
| Myalgia | | | |
| subjects affected / exposed | 24 / 954 (2.52%) | | |
| occurrences (all) | 28 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 26 / 954 (2.73%) | | |
| occurrences (all) | 33 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 71 / 954 (7.44%) | | |
| occurrences (all) | 105 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 23 / 954 (2.41%) | | |
| occurrences (all) | 30 | | |
| Influenza | | | |
| subjects affected / exposed | 36 / 954 (3.77%) | | |
| occurrences (all) | 42 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 56 / 954 (5.87%) | | |
| occurrences (all) | 78 | | |
| Pneumonia | | | |
| subjects affected / exposed | 22 / 954 (2.31%) | | |
| occurrences (all) | 24 | | |
| Urinary tract infection | | | |

| | | | |
|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Upper respiratory tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>COVID-19</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>73 / 954 (7.65%)</p> <p>130</p> <p>34 / 954 (3.56%)</p> <p>40</p> <p>6 / 954 (0.63%)</p> <p>6</p> | | |
| <p>Metabolism and nutrition disorders</p> <p>Hyperkalaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypokalaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>22 / 954 (2.31%)</p> <p>32</p> <p>12 / 954 (1.26%)</p> <p>13</p> <p>40 / 954 (4.19%)</p> <p>49</p> | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 November 2014 | Main modifications: • The definition of progression in soft tissue was clarified, excluding progression in lymph nodes in the pelvis below the aortic bifurcation. • An inclusion criterion related to PSA values was amended to allow patients with CRPC defined as "3 rising PSA values at least 1 week apart during ADT" to enter the study. The observation period of PSA values that could be used in the calculation of PSADT was prolonged from 6 to 12 months. • PFS was added as an additional exploratory endpoint. • The collection period of pain data was corrected to continue until documented pain progression and question 7 of Brief Pain Inventory-Short form (BPI-SF) was deleted. The pain medication data was to be collected using case report forms (CRFs) only. • The 3 consecutive blood pressure, heart rate, and electrocardiogram (ECG) recordings were amended to be performed within approximately 5 minutes. • Suspected disease progression was added as a reason for an unscheduled visit. Chest, abdomen and pelvic CT/MRI or x-ray and bone scan were added as options for assessments that could be performed at the unscheduled visit, if indicated. • Use of antineoplastic therapies was clarified. An instruction was added that another systemic antineoplastic therapy could be initiated no sooner than 7 days after the last dose of study treatment. The end-of-study treatment visit was changed to take place 28 days after the last dose (instead of 7 days) for patients who permanently discontinue study treatment and start subsequent antineoplastic therapy. • It was clarified to exclude patients using osteoclast-targeted therapy for prevention of skeletal-related events and to allow those using this therapy for osteoporosis at a dose and schedule indicated for osteoporosis. The minimum duration of this therapy for osteoporosis was deleted. • Withdrawal at the investigator's discretion was added as a reason for discontinuation. |
| 19 July 2016 | The protocol was updated to reflect the sponsorship change from Orion to Bayer, and to update information about the study number and study drug nomenclature. Other main modifications were: • Clarifications on inclusion and exclusion criteria were made. • Requirements for monitoring drug-drug interactions were revised. |
| 26 February 2018 | Main modifications: • The assumption for the treatment effect size of a hazard ratio of 0.75 requiring 572 MFS events was revised and changed to a larger assumed treatment effect size of 0.65 requiring approximately 385 MFS events. Statistical analyses of primary and secondary endpoints were also modified. The analysis of the primary efficacy endpoint was referred to as MFS analysis throughout the protocol. It was also clarified that secondary endpoints are to be evaluated at the time of the MFS analysis, and at a later time point. • The possibility to receive open-label darolutamide treatment was added, to allow patients who are on darolutamide/placebo treatment at the time of study treatment code unblinding to continue open-label darolutamide treatment at the discretion of the investigator, if the study results support a positive benefit/risk assessment for darolutamide in the study by judgment of the sponsor (considering feedback from the study steering committee and/or health authorities). • Assessments for patients who continue on open-label darolutamide treatment were added. • A standard guidance text was added stating that recording of contrast media as concomitant medication is not required unless there was an AE related to its administration. • Additional survival sweeps were added, to occur shortly after the database cut-off date for the MFS analysis and prior to any subsequent analysis of OS to ensure that OS data are current. |

| | |
|--------------|---|
| 06 July 2019 | <p>Main modifications:</p> <ul style="list-style-type: none"> • The option for patients currently receiving treatment in this study to continue treatment in a roll-over study and respective statistical considerations were added to enable patients receiving darolutamide treatment continue to receive darolutamide treatment when the study is completed. The end of study was also defined for completeness and clarity. • The recommendation to avoid concomitant use of moderate CYP3A4 inducers was removed (while strong CYP3A4 inducers should still be avoided). Recent results of the darolutamide exposure-response relationship showed a flat relationship (maximum PSA response) over the entire exposure range of 600 mg b.i.d. and also at exposures below that range. Thus, even with a darolutamide exposure decrease of 50% (potentially driven by a CYP3A4 inducer), there would still be sufficient effect on PSA. • Open-label study wording was updated to describe the endpoint of the study visits and follow up, to describe the local and central reading requirements for metastasis assessments, to add guidance related to discontinuation of study treatment and to clarify the time points of ECG collection. |
|--------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported