# Clinical trial results:
# Multinational, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients With Metastatic Hormone Sensitive Prostate Cancer (mHSPC)

## Summary

| | |
|---|---|
| EudraCT number | 2015-003869-28 |
| Trial protocol | NL BE ES DK FI SE DE SK GB FR IT |
| Global end of trial date | |

### Results information

| | |
|---|---|
| Result version number | v3 |
| This version publication date | 13 June 2025 |
| First version publication date | 23 April 2020 |
| Version creation reason | |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 9785-CL-0335 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02677896 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Astellas Pharma Global Development, Inc. (APGD) |
| Sponsor organisation address | 1 Astellas Way, Northbrook, IL, United States, 60062 |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), astellas.resultsdisclosure@astellas.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 | Interim |
| Date of interim/final analysis | 28 May 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by radiographic progression-free survival (rPFS) based on independent central review (ICR).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 March 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 31 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Japan: 92 |
| Country: Number of subjects enrolled | Taiwan: 30 |
| Country: Number of subjects enrolled | Korea, Republic of: 25 |
| Country: Number of subjects enrolled | Australia: 47 |
| Country: Number of subjects enrolled | New Zealand: 23 |
| Country: Number of subjects enrolled | Russian Federation: 139 |
| Country: Number of subjects enrolled | Slovakia: 81 |
| Country: Number of subjects enrolled | Italy: 68 |
| Country: Number of subjects enrolled | Denmark: 62 |
| Country: Number of subjects enrolled | Romania: 57 |
| Country: Number of subjects enrolled | Spain: 55 |
| Country: Number of subjects enrolled | Netherlands: 54 |
| Country: Number of subjects enrolled | Poland: 47 |
| Country: Number of subjects enrolled | France: 44 |
| Country: Number of subjects enrolled | Finland: 39 |
| Country: Number of subjects enrolled | Belgium: 15 |

| | |
|---|---|
| Country: Number of subjects enrolled | Sweden: 12 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | United States: 122 |
| Country: Number of subjects enrolled | Canada: 41 |
| Country: Number of subjects enrolled | Argentina: 10 |
| Country: Number of subjects enrolled | Chile: 52 |
| Country: Number of subjects enrolled | Israel: 23 |
| Worldwide total number of subjects | 1150 |
| EEA total number of subjects | 544 |

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) | 300 |
| From 65 to 84 years | 824 |
| 85 years and over | 26 |

## Subject disposition

### Recruitment

Recruitment details:

Participants with metastatic hormone sensitive prostate cancer (mHSPC) were enrolled in 204 study sites worldwide.

### Pre-assignment

Screening details:

The randomization was stratified by volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1 to 5 cycles, 6 cycles).

### Period 1

| | |
|---|---|
| Period 1 title | Double Blind Period (up to 35 months) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Enzalutamide + Androgen Deprivation Therapy (ADT) |

Arm description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Enzalutamide |
| Investigational medicinal product code | MDV3100 |
| Other name | Xtandi |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 4 capsules (40 mg each) of enzalutamide orally once a day, for a total daily dose of 160 mg. Treatment was given with or without food and as close as possible to the same time each day.

| | |
|---|---|
| **Arm title** | Placebo + Androgen Deprivation Therapy (ADT) |

Arm description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

| | |
|---|---|
| Arm type | Placebo |

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 4 capsules of matching placebo orally once a day. Treatment was given with or without food and as close as possible to the same time each day.

| **Number of subjects in period 1** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy (ADT) |
|---|---|---|
| Started | 574 | 576 |
| Completed | 0 | 0 |
| Not completed | 574 | 576 |
| Adverse event, serious fatal | 117 | 197 |
| Randomized, Not Treated | - | 2 |
| Consent withdrawn by subject | 41 | 71 |
| Discontinued by Sponsor | 1 | 4 |
| Progressive Disease | 3 | 6 |
| Miscellaneous | 30 | 99 |
| Lost to follow-up | 12 | 15 |
| Continued in OLE | 370 | 182 |

## Period 2

| | |
|---|---|
| Period 2 title | Open-Label Extension (approx. 66 months) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Enzalutamide + Androgen Deprivation Therapy (ADT) |

Arm description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Enzalutamide |
| Investigational medicinal product code | MDV3100 |
| Other name | Xtandi |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 4 capsules (40 mg each) of enzalutamide orally once a day, for a total daily dose of 160 mg. Treatment was given with or without food and as close as possible to the same time each day.

| | |
|---|---|
| **Arm title** | Placebo + Androgen Deprivation Therapy (ADT) |

Arm description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site's pharmacy stock.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Enzalutamide |
| Investigational medicinal product code | MDV3100 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 4 capsules (40 mg each) of enzalutamide orally once a day, for a total daily dose of 160 mg. Treatment was given with or without food and as close as possible to the same time each day.

| **Number of subjects in period 2** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy (ADT) |
|---|---|---|
| Started | 370 | 182 |
| Completed | 0 | 0 |
| Not completed | 370 | 182 |
| Adverse event, serious fatal | 73 | 26 |
| Consent withdrawn by subject | 16 | 13 |
| Discontinued by Sponsor | 10 | 5 |
| Progressive Disease | 22 | 10 |
| Miscellaneous | 241 | 125 |
| Lost to follow-up | 8 | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Enzalutamide + Androgen Deprivation Therapy (ADT) |

Reporting group description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site's pharmacy stock.

| Reporting group title | Placebo + Androgen Deprivation Therapy (ADT) |
|---|---|

Reporting group description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site's pharmacy stock.

| Reporting group values | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy (ADT) | Total |
|---|---|---|---|
| Number of subjects | 574 | 576 | 1150 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| All randomized participants. | | | |
| Units: years | | | |
| arithmetic mean | 69.5 | 69.5 | |
| standard deviation | ± 8 | ± 8.4 | - |
| Gender categorical | | | |
| All randomized participants. | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 574 | 576 | 1150 |
| Race (NIH/OMB) | | | |
| All randomized participants. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 75 | 80 | 155 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 8 | 8 | 16 |
| White | 466 | 460 | 926 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 25 | 28 | 53 |

| Ethnicity (NIH/OMB) | | | |
|---|---|---|---|
| All randomized participants. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 46 | 37 | 83 |
| Not Hispanic or Latino | 504 | 514 | 1018 |
| Unknown or Not Reported | 24 | 25 | 49 |
| Volume of Disease | | | |
| High volume of disease was defined as metastases involving the viscera or, in the absence of visceral lesions, 4 or more bone lesions, at least 1 of which was in a bony structure beyond the vertebral column and pelvic bone. Low volume was anything that wasn't considered high volume by definition provided. Intent-to-Treat (ITT) population is defined as all participants who were randomized in this study. | | | |
| Units: Subjects | | | |
| Low | 220 | 203 | 423 |
| High | 354 | 373 | 727 |
| Prior Docetaxel Therapy Use | | | |
| ITT | | | |
| Units: Subjects | | | |
| None | 471 | 474 | 945 |
| 1 to 5 cycles | 14 | 11 | 25 |
| 6 cycles | 89 | 91 | 180 |

## End points

### End points reporting groups

| Reporting group title | Enzalutamide + Androgen Deprivation Therapy (ADT) |
|---|---|

Reporting group description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

| Reporting group title | Placebo + Androgen Deprivation Therapy (ADT) |
|---|---|

Reporting group description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

| Reporting group title | Enzalutamide + Androgen Deprivation Therapy (ADT) |
|---|---|

Reporting group description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

| Reporting group title | Placebo + Androgen Deprivation Therapy (ADT) |
|---|---|

Reporting group description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

| Subject analysis set title | Enzalutamide + Androgen Deprivation Therapy (ADT) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants received 160 mg of enzalutamide orally once daily during double blind treatment period until radiographic progression was documented or until the Participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site’s pharmacy stock.

| Subject analysis set title | Placebo + Androgen Deprivation Therapy |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants received enzalutamide matching placebo orally once daily during double blind treatment period until radiographic progression was documented or until the Participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide matching placebo during double blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site's pharmacy stock.

## Primary: Radiographic Progression-Free Survival (rPFS) Based on Independent Central Review (ICR) of Bone Scan According to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) Criteria

| | |
|---|---|
| End point title | Radiographic Progression-Free Survival (rPFS) Based on Independent Central Review (ICR) of Bone Scan According to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) Criteria |

End point description:

rPFS was calculated as the time from the date of randomization to the first objective evidence of radiographic progression disease (rPD) at any time or death up to 24 weeks after study drug discontinuation without documented radiographic progression, whichever occurred first. rPD was defined as progressive disease by RECIST version 1.1 for soft tissue disease or by appearance of 2 or more new lesions on bone scan compared to baseline or week 13 according to PCWG2 criteria, as assessed by ICR or death. In participants with no rPFS event, rPFS was censored on the date of last evaluable radiographic assessment prior to the data analysis cutoff date. In participants with no baseline radiographic assessment, participants with no postbaseline radiographic assessments and participants with all postbaseline radiographic assessments documented as "not evaluable (NE)," rPFS was censored on the date of randomization. ITT population. "99999" denotes data not reached due to low number of events.

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

End point timeframe:

From the date of randomization to the first objective evidence of rPD at any time or death (maximum duration was 26.6 months)

| **End point values** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 574 | 576 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| months | 99999 (99999 to 99999) | 19.4 (16.59 to 99999) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|

Statistical analysis description:

rPFS Treatment Comparison

| | |
|---|---|
| Comparison groups | Placebo + Androgen Deprivation Therapy v Enzalutamide + Androgen Deprivation Therapy (ADT) |

| | |
|---|---|
| Number of subjects included in analysis | 1150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [1] |
| Method | Logrank |
| Parameter estimate | Cox hazard ratio |
| Point estimate | 0.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 0.5 |

Notes:

[1] - Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no) during screening period.

## Primary: rPFS Based on ICR of Bone Scan According to Protocol Assessment Criteria

| | |
|---|---|
| End point title | rPFS Based on ICR of Bone Scan According to Protocol Assessment Criteria |

End point description:

rPFS was calculated as the time from the date of randomization to the first objective evidence of rPD at any time or death up to 24 weeks after study drug discontinuation without documented radiographic progression, whichever occurred first. rPD was defined as progressive disease by RECIST version 1.1 for soft tissue disease or by appearance of 2 or more new lesions on bone scan compared to baseline for week 13 or the best response on treatment for week 25 or later assessments, as assessed by ICR or death. In participants with no rPFS event, rPFS was censored on the date of last evaluable radiographic assessment prior to the data analysis cutoff date. In participants with no baseline radiographic assessment, participants with no postbaseline radiographic assessments & participants with all postbaseline radiographic assessments documented as "not evaluable(NE)," rPFS was censored on the date of randomization.ITT population."99999" denotes data not reached due to low number of events.

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

End point timeframe:

From the date of randomization to the first objective evidence of rPD at any time or death (maximum duration was 26.6 months)

| **End point values** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 574 | 576 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| months | 99999 (99999 to 99999) | 19.0 (16.59 to 22.24) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|

Statistical analysis description:

rPFS Treatment Comparision

| | |
|---|---|
| Comparison groups | Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy |
| Number of subjects included in analysis | 1150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Cox proportional hazards model |
| Point estimate | 0.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 0.5 |

## Secondary: Overall Survival (OS)

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

End point description:

OS was defined as the time from randomization to death due to any cause. In participants still alive at the date of the analysis cutoff point, OS was censored on the last date the participant was known to be alive. OS was analyzed using Kaplan-Meier estimates. ITT population

99999 denotes data was not reached due to low number of events.

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

End point timeframe:

From randomization to death due to any cause (maximum duration was 58.6 months)

| End point values | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 574 | 576 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (49.74 to 99999) | | |

## Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical Analysis 1 |
| Comparison groups | Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy |

| | |
|---|---|
| Number of subjects included in analysis | 1150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | < 0.0001 [3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.53 |
| upper limit | 0.81 |

Notes:

[2] - Significance level is 0.04. Hazard ratio and 95 % CI are estimated by cox proportional hazards model.
[3] - P-value from stratified log-rank test.

## Secondary: Time to Start of New Antineoplastic Therapy

| | |
|---|---|
| End point title | Time to Start of New Antineoplastic Therapy |

End point description:

In participants with a new antineoplastic therapy initiated for prostate cancer after randomization, time to start of a new antineoplastic therapy was defined as the time interval from randomization to the date of the first dose administration of the first antineoplastic therapy. In participants with no new antineoplastic therapy initiated for prostate cancer after randomization, time to start of new antineoplastic therapy was censored on the last visit date or the date of randomization, whichever occurred last. ITT population. 99999 denotes data not reached due to low number of events. Time to start of new antineoplastic therapy was analyzed using Kaplan-Meier estimates.

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

End point timeframe:

From randomization to the date of the first dose administration of the first antineoplastic therapy (maximum duration was 58.6 months)

| **End point values** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 574 | 576 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| months | 99999 (99999 to 99999) | 40.5 (26.25 to 99999) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy |

| | |
|---|---|
| Number of subjects included in analysis | 1150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.31 |
| upper limit | 0.48 |

Notes:

[4] - Hazard ratio and 95 % CI are estimated by cox proportional hazards model.

## Secondary: Time to Prostate Specific Antigen (PSA) Progression

| | |
|---|---|
| End point title | Time to Prostate Specific Antigen (PSA) Progression |

End point description:

Time to PSA progression was calculated as the time from the date of randomization to the first observation of PSA progression. A PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir, which was confirmed by a second consecutive value at least 3 weeks later. In participants with no PSA progression, time to PSA progression was censored on the date of the last PSA sample taken (or last value prior to 2 or more consecutive missed PSA assessments). ITT population. "99999" denotes data not reached due to low number of events.

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

End point timeframe:

From the date of randomization to the first observation of PSA progression (maximum duration was 26.6 months)

| **End point values** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 574 | 576 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| months | 99999 (99999 to 99999) | 99999 (16.59 to 99999) | | |

### Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|

Statistical analysis description:

Time to PSA Progression Treatment Comparison

| | |
|---|---|
| Comparison groups | Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy |

| | |
|---|---|
| Number of subjects included in analysis | 1150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [5] |
| Method | Logrank |
| Parameter estimate | Cox hazard ratio |
| Point estimate | 0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.13 |
| upper limit | 0.26 |

Notes:

[5] - Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no) during screening period.

## Secondary: PSA Undetectable Rate

| | |
|---|---|
| End point title | PSA Undetectable Rate |

End point description:

The PSA undetectable rate was defined as the percentage of participants with undetectable (< 0.2 ng/mL) PSA values at any time during study treatment, of those participants with detectable (≥ 0.2 ng/mL) PSA values at baseline. ITT with detectable PSA at baseline.

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

End point timeframe:

From baseline to detectable PSA values (maximum duration was 26.6 months)

| **End point values** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 511 | 506 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| percentage of participants | 68.1 (63.9 to 72.1) | 17.6 (14.4 to 21.2) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|

Statistical analysis description:

PSA Undetectable Rate Treatment Comparison

| | |
|---|---|
| Comparison groups | Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy |

| | |
|---|---|
| Number of subjects included in analysis | 1017 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in rate |
| Point estimate | 50.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 45.3 |
| upper limit | 55.7 |

Notes:

[6] - Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no) during screening period.

## Secondary: Objective Response Rate (ORR)

| | |
|---|---|
| End point title | Objective Response Rate (ORR) |

End point description:

The ORR was calculated as the percentage of participants who achieved a completed response (CR) or a partial response (PR) (unconfirmed responses) in their soft tissue disease using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 assessed by ICR. ITT participants with measurable disease at baseline.

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

End point timeframe:

From date of randomization up to 26.6 months

| End point values | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 177 | 182 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| percentage of participants | 83.1 (76.7 to 88.3) | 63.7 (56.3 to 70.7) | | |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|

Statistical analysis description:

ORR Treatment Comparison

| | |
|---|---|
| Comparison groups | Placebo + Androgen Deprivation Therapy v Enzalutamide + Androgen Deprivation Therapy (ADT) |

| | |
|---|---|
| Number of subjects included in analysis | 359 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [7] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in rate |
| Point estimate | 19.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.4 |
| upper limit | 28.2 |

Notes:

[7] - Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no) during screening period.

## Secondary: Time to First Symptomatic Skeletal Event (SSE)

| | |
|---|---|
| End point title | Time to First Symptomatic Skeletal Event (SSE) |

End point description:

Time to first SSE was calculated as the time from randomization to the occurrence of the first SSE. An SSE was defined as radiation to bone, surgery to bone, clinically apparent pathological bone fracture, or spinal cord compression. In participants with no SSE, time to SSE was censored on the last visit date or the date of randomization, whichever occurred last.

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

End point timeframe:

From randomization to the occurrence of the first SSE (maximum duration was 26.6 months)

| **End point values** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 574 | 576 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| months | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

### Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|

Statistical analysis description:

Time to SSE Treatment Comparison

| | |
|---|---|
| Comparison groups | Placebo + Androgen Deprivation Therapy v Enzalutamide + Androgen Deprivation Therapy (ADT) |

| | |
|---|---|
| Number of subjects included in analysis | 1150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0026 |
| Method | Logrank |
| Parameter estimate | Cox hazard ratio |
| Point estimate | 0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.33 |
| upper limit | 0.8 |

## Secondary: Time to Deterioration in Urinary Symptoms

| | |
|---|---|
| End point title | Time to Deterioration in Urinary Symptoms |

End point description:

In participants with deterioration, time to deterioration was calculated as the time interval between randomization and the first deterioration in urinary symptoms at any postbaseline visit. Deterioration in urinary symptoms was defined as an increase in the Quality of Life Prostate-specific Questionnaire(QLQ-PR25) modified urinary symptoms. Subscale score by ≥50% of the standard deviation observed in the QLQ-PR25 modified urinary symptoms subscale score at baseline. Modified urinary symptoms subscale score consisted of 3-items(Q31–Q33) from the QLQ-PR25,each scored from 1(not at all) to 4(very much). Total modified urinary symptoms subscale score ranges from 0-100,higher scores represents a higher level of symptomatology/problems. In participants without deterioration in urinary symptoms, the time to deterioration in urinary symptoms was censored on the date the last urinary symptoms QLQ-PR25 score was calculable. ITT. "99999" denotes data not reached due to low number of events.

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

End point timeframe:

From date of randomization to the first deterioration in urinary symptoms at any postbaseline visit (maximum duration was 26.6 months)

| **End point values** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 574 | 576 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| months | 99999 (19.35 to 99999) | 16.8 (14.06 to 99999) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|

Statistical analysis description:

Time to Deterioration of Urinary Symptoms Treatment Comparison

| | |
|---|---|
| Comparison groups | Placebo + Androgen Deprivation Therapy v Enzalutamide + |

| | Androgen Deprivation Therapy (ADT) |
|---|---|
| Number of subjects included in analysis | 1150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2162 [8] |
| Method | Logrank |
| Parameter estimate | Cox hazard ratio |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.08 |

Notes:

[8] - Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no) during screening period.

## Secondary: Time to Deterioration of Quality of Life (QoL) in Functional Assessment of Cancer Therapy-Prostate (FACT-P)

| End point title | Time to Deterioration of Quality of Life (QoL) in Functional Assessment of Cancer Therapy-Prostate (FACT-P) |
|---|---|

End point description:

Time to deterioration of QoL was calculated as the time interval from the date of randomization to the first date a decline from baseline of 10 points or more in the FACT-P total score was recorded. The FACT-P consists of 27 core items that assess participant function in 4 domains and 12 prostate cancer-related items grouped into 5 subscales as follows: physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing and prostate cancer subscale. Each item is rated on a 0 to 4 Likert-type scale. The FACT-P total score is the sum of all 5 subscale scores of the FACT-P questionnaire and ranges from 0 to 156), where high score represent better quality of life. In participants without FACT-P progression, the time to deterioration of QoL was censored on the date of the last FACT-P total score was calculable. ITT population.

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

End point timeframe:

From the date of randomization to the first date a decline from baseline of 10 points or more in the FACT-P total score (maximum duration was 26.6 months)

| **End point values** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 574 | 576 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| months | 11.3 (11.04 to 13.83) | 11.1 (8.48 to 13.83) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|

| Statistical analysis description: | |
|---|---|
| Time to Deterioration of QoL in FACT-P Treatment Comparison | |
| Comparison groups | Placebo + Androgen Deprivation Therapy v Enzalutamide + Androgen Deprivation Therapy (ADT) |
| Number of subjects included in analysis | 1150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6548 |
| Method | Logrank |
| Parameter estimate | Cox hazard ratio |
| Point estimate | 0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.14 |

## Secondary: Time to Castration Resistance

| End point title | Time to Castration Resistance |
|---|---|

End point description:

Time to castration resistance was calculated as the time from randomization to the first castration-resistant event. A castration resistance event was defined as any of the following in the presence of castrate levels of testosterone (< 50 ng/dL): radiographic disease progression, PSA progression or SSE, whichever occurred first. In participants with no documented castration resistance event, the time to castration resistance was censored on the latest date from: the date of last radiologic assessment, the last PSA sample taken prior to the start of any new prostate cancer therapy and prior to 2 or more consecutive missed PSA assessments (if applicable), and the last visit date performed. ITT population. "99999" denotes data not reached due to low number of events.

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

End point timeframe:

From randomization to the first castration-resistant event (maximum duration was 26.6 months)

| End point values | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 574 | 576 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| months | 99999 (99999 to 99999) | 13.9 (11.40 to 17.18) | | |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|

| | |
|---|---|
| Statistical analysis description: | |
| Time to Castration Resistance Treatment Comparison | |
| Comparison groups | Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy |
| Number of subjects included in analysis | 1150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Cox hazard ratio |
| Point estimate | 0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.22 |
| upper limit | 0.36 |

## Secondary: Time to Pain Progression Based on Brief Pain Inventory-Short Form (BPI-SF)

| | |
|---|---|
| End point title | Time to Pain Progression Based on Brief Pain Inventory-Short Form (BPI-SF) |

End point description:

Time to pain progression was defined as time from randomization to the first pain progression event. Pain progression was defined as an increase of ≥ 30% from baseline in the average BPI-SF pain severity score. BPI-SF contains 9 questions with rating scales from 0 (no pain/no interference) to 10 (worst pain/interferes completely). Total score was calculated as the average of each question. Higher scores represent a higher level of pain or interference. In participants with no pain progression event, time to pain progression was censored on the last visit date where BPI-SF was collected. ITT population.

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

End point timeframe:

From randomization to the first pain progression event (maximum duration was 26.6 months)

| **End point values** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo + Androgen Deprivation Therapy | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 574 | 576 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| months | 8.3 (8.25 to 10.91) | 8.3 (5.65 to 8.38) | | |

## Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical analysis 1 |

Statistical analysis description:

Time to Pain Progression Based on BPI-SF Treatment Comparison

| | |
|---|---|
| Comparison groups | Enzalutamide + Androgen Deprivation Therapy (ADT) v Placebo + Androgen Deprivation Therapy |
| Number of subjects included in analysis | 1150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2715 |
| Method | Logrank |
| Parameter estimate | Cox hazard ratio |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 1.07 |

## Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: From randomization up to end of study duration (approximately 8 years)
AEs: From first dose up to 30 days after last dose of study drug (maximum duration of treatment 7 years)

Adverse event reporting additional description:

All-cause mortality: All randomized participants

Safety Analysis Set (SAF) consisted of all randomized participants who received at least one dose of study drug.

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

## Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | v26 |

## Reporting groups

| | |
|---|---|
| Reporting group title | Enzalutamide + Androgen Deprivation Therapy (ADT) |

Reporting group description:

Participants received 160 mg of enzalutamide orally once daily during double-blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Eligible participants who received enzalutamide during double-blind treatment period and provided informed consent to take part in open-label period continued to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site's pharmacy stock.

| | |
|---|---|
| Reporting group title | Placebo cross-over Enzalutamide |

Reporting group description:

Eligible participants who received enzalutamide matching placebo during double-blind treatment period and provided informed consent to take part in open-label period switched to receive 160 mg enzalutamide orally once daily in open-label period until disease progression, unacceptable toxicity or any other discontinuation criteria were met. ADT (either bilateral orchiectomy or LHRH agonist/antagonist) was maintained during study treatment as per standard of care and provided by the site's pharmacy stock. This arm represents only the open-label extension period.

| | |
|---|---|
| Reporting group title | Placebo + ADT |

Reporting group description:

Participants received enzalutamide matching placebo orally once daily during double-blind treatment period until radiographic progression was documented or until the participants started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. This arm represents only double blind period.

| **Serious adverse events** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo cross-over Enzalutamide | Placebo + ADT |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 244 / 572 (42.66%) | 81 / 182 (44.51%) | 128 / 574 (22.30%) |
| number of deaths (all causes) | 191 | 27 | 197 |
| number of deaths resulting from adverse events | 48 | 13 | 12 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|---|---|---|
| Bone cancer | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 cancer | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Benign pancreatic neoplasm | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 6 / 572 (1.05%) | 2 / 182 (1.10%) | 5 / 574 (0.87%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 13 / 572 (2.27%) | 4 / 182 (2.20%) | 3 / 574 (0.52%) |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 6 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 9 | 0 / 3 | 0 / 2 |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm malignant | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 572 (0.87%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Lung adenocarcinoma stage I | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 adenocarcinoma stage 0 | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to liver | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Laryngeal squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Colon cancer | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 3 / 574 (0.52%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Monoclonal gammopathy | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine carcinoma | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Paraproteinaemia | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plasmacytoma | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| 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 / 572 (0.17%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of head and neck | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| 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 of skin | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Bowen's disease | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Meningioma | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Metastases to adrenals | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 central nervous system | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Oesophageal squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Penile cancer | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 cancer metastatic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Lip squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 lung neoplasm | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cancer | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Soft tissue sarcoma | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic dissection | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 0 / 182 (0.00%) | 0 / 574 (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 dissection rupture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 3 / 182 (1.65%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 7 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Granulomatosis with polyangiitis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 embolism | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Haematoma | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Essential hypertension | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Embolism arterial | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 venous | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Haemodynamic instability | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 artery occlusion | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 artery thrombosis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | | | |
| Euthanasia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Bone lesion excision | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 2 / 182 (1.10%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 1 / 1 |
| Fatigue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 572 (0.70%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chills | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Drowning | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| Implant site dehiscence | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Social circumstances | | | |
| Loss of personal independence in daily activities | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Reproductive system and breast disorders | | | |

| | | | |
|---|---|---|---|
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 2 / 182 (1.10%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 6 / 572 (1.05%) | 5 / 182 (2.75%) | 3 / 574 (0.52%) |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 6 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |

| | | | |
|---|---|---|---|
| Hypoxia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Eosinophilic pneumonia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Diaphragmatic paralysis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 haemorrhage | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 respiratory failure | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pleural effusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Pneumomediastinum | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Product issues | | | |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 testosterone increased | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Aspartate aminotransferase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Antineutrophil cytoplasmic antibody increased | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone fissure | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Comminuted fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 restenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| 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 | 12 / 572 (2.10%) | 2 / 182 (1.10%) | 4 / 574 (0.70%) |
| occurrences causally related to treatment / all | 4 / 12 | 2 / 2 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 4 / 572 (0.70%) | 2 / 182 (1.10%) | 3 / 574 (0.52%) |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 3 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture displacement | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract stoma complication | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 postoperative | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thoracic vertebral fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery restenosis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 fractures | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stenosis of vesicourethral anastomosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain contusion | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Jaw fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 6 / 572 (1.05%) | 2 / 182 (1.10%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Infusion related reaction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Concussion | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound haemorrhage | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Overdose | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Scapula fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Skull fractured base | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 4 / 572 (0.70%) | 3 / 182 (1.65%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrong dose | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Flail chest | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 limb fracture | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periprosthetic fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 4 / 572 (0.70%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Atrioventricular block | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 10 / 572 (1.75%) | 2 / 182 (1.10%) | 7 / 574 (1.22%) |
| occurrences causally related to treatment / all | 3 / 13 | 0 / 2 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure chronic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 5 / 572 (0.87%) | 2 / 182 (1.10%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 1 / 5 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 6 / 572 (1.05%) | 2 / 182 (1.10%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 2 / 8 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 2 / 182 (1.10%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Acute myocardial infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 572 (0.70%) | 2 / 182 (1.10%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 4 / 572 (0.70%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 2 / 182 (1.10%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Trifascicular block | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Supraventricular tachycardia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 / 572 (0.17%) | 2 / 182 (1.10%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac pseudoaneurysm | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Nervous system disorders | | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid arteriosclerosis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Cerebellar infarction | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 5 / 572 (0.87%) | 3 / 182 (1.65%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 2 / 6 | 3 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| Transient global amnesia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Toxic encephalopathy | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 5 / 572 (0.87%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 1 / 182 (0.55%) | 7 / 574 (1.22%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 0 / 182 (0.00%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraparesis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Monoparesis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Dementia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 4 / 572 (0.70%) | 1 / 182 (0.55%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Altered state of consciousness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Aphasia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Brain stem haemorrhage | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Cerebral infarction | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paralysis | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Hemianopia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Hypoglycaemic seizure | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Thalamus haemorrhage | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral artery stenosis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Myelopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Nerve compression | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 572 (1.22%) | 1 / 182 (0.55%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood loss anaemia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune thrombocytopenia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 6 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency anaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Pancytopenia | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Deafness neurosensory | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Meniere's disease | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Vertigo | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Ulcerative keratitis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal detachment | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye haemorrhage | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Cataract | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 5 / 182 (2.75%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epiretinal membrane | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Epiploic appendagitis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Duodenitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Duodenal ulcer perforation | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ischaemic | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| 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 | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 0 / 182 (0.00%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retroperitoneal fibrosis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Nausea | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Inguinal hernia | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Mesenteric artery stenosis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 ulcer | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Ascites | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | | | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 3 / 182 (1.65%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Bile duct stone | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Panniculitis | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 colic | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Hydronephrosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 572 (0.70%) | 1 / 182 (0.55%) | 3 / 574 (0.52%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 9 / 572 (1.57%) | 1 / 182 (0.55%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysuria | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Calculus bladder | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 7 / 572 (1.22%) | 1 / 182 (0.55%) | 3 / 574 (0.52%) |
| occurrences causally related to treatment / all | 3 / 11 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Bladder perforation | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Urethral obstruction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethral stenosis | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 9 / 572 (1.57%) | 2 / 182 (1.10%) | 4 / 574 (0.70%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Urinary incontinence | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Urinary bladder haemorrhage | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Bladder mass | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Chronic kidney disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 2 / 182 (1.10%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 0 / 182 (0.00%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Arthritis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Compartment syndrome | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Flank pain | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Infections and infestations | | | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anorectal infection | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 572 (0.52%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia pyelonephritis | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 2 / 182 (1.10%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Genital abscess | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin abscess | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected lymphocele | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Otitis media chronic | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 9 / 572 (1.57%) | 1 / 182 (0.55%) | 5 / 574 (0.87%) |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 1 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 4 / 572 (0.70%) | 2 / 182 (1.10%) | 3 / 574 (0.52%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 7 / 572 (1.22%) | 2 / 182 (1.10%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| COVID-19 pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 572 (0.52%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Gangrene | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Spinal cord infection | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Systemic candida | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 staphylococcal | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Oral infection | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Mycobacterium avium complex infection | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Diabetic gangrene | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 572 (0.35%) | 1 / 182 (0.55%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cachexia | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 0 / 182 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adult failure to thrive | | | |
| subjects affected / exposed | 1 / 572 (0.17%) | 0 / 182 (0.00%) | 0 / 574 (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 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 572 (0.35%) | 0 / 182 (0.00%) | 0 / 574 (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 inadequate control | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 572 (0.00%) | 1 / 182 (0.55%) | 0 / 574 (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 |

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

| **Non-serious adverse events** | Enzalutamide + Androgen Deprivation Therapy (ADT) | Placebo cross-over Enzalutamide | Placebo + ADT |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 463 / 572 (80.94%) | 133 / 182 (73.08%) | 401 / 574 (69.86%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 88 / 572 (15.38%) | 19 / 182 (10.44%) | 36 / 574 (6.27%) |
| occurrences (all) | 107 | 22 | 38 |
| Hot flush | | | |
| subjects affected / exposed | 172 / 572 (30.07%) | 16 / 182 (8.79%) | 131 / 574 (22.82%) |
| occurrences (all) | 199 | 18 | 137 |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 51 / 572 (8.92%) | 8 / 182 (4.40%) | 40 / 574 (6.97%) |
| occurrences (all) | 66 | 9 | 48 |
| Fatigue | | | |
| subjects affected / exposed | 147 / 572 (25.70%) | 43 / 182 (23.63%) | 92 / 574 (16.03%) |
| occurrences (all) | 197 | 54 | 103 |
| Asthenia | | | |
| subjects affected / exposed | 52 / 572 (9.09%) | 6 / 182 (3.30%) | 29 / 574 (5.05%) |
| occurrences (all) | 79 | 7 | 36 |
| Reproductive system and breast disorders | | | |
| Gynaecomastia | | | |
| subjects affected / exposed | 34 / 572 (5.94%) | 4 / 182 (2.20%) | 8 / 574 (1.39%) |
| occurrences (all) | 39 | 4 | 8 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 32 / 572 (5.59%) | 6 / 182 (3.30%) | 21 / 574 (3.66%) |
| occurrences (all) | 36 | 6 | 22 |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 46 / 572 (8.04%) | 2 / 182 (1.10%) | 45 / 574 (7.84%) |
| occurrences (all) | 89 | 2 | 51 |
| Weight decreased | | | |
| subjects affected / exposed | 30 / 572 (5.24%) | 14 / 182 (7.69%) | 16 / 574 (2.79%) |
| occurrences (all) | 39 | 15 | 17 |
| Injury, poisoning and procedural | | | |

| | | | |
|---|---|---|---|
| complications | | | |
| Fall | | | |
| subjects affected / exposed | 63 / 572 (11.01%) | 19 / 182 (10.44%) | 16 / 574 (2.79%) |
| occurrences (all) | 96 | 30 | 16 |
| Rib fracture | | | |
| subjects affected / exposed | 38 / 572 (6.64%) | 12 / 182 (6.59%) | 6 / 574 (1.05%) |
| occurrences (all) | 47 | 18 | 8 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 52 / 572 (9.09%) | 8 / 182 (4.40%) | 22 / 574 (3.83%) |
| occurrences (all) | 62 | 9 | 27 |
| Dizziness | | | |
| subjects affected / exposed | 47 / 572 (8.22%) | 9 / 182 (4.95%) | 22 / 574 (3.83%) |
| occurrences (all) | 50 | 9 | 24 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 51 / 572 (8.92%) | 5 / 182 (2.75%) | 28 / 574 (4.88%) |
| occurrences (all) | 86 | 6 | 39 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 54 / 572 (9.44%) | 14 / 182 (7.69%) | 34 / 574 (5.92%) |
| occurrences (all) | 65 | 19 | 35 |
| Diarrhoea | | | |
| subjects affected / exposed | 56 / 572 (9.79%) | 9 / 182 (4.95%) | 34 / 574 (5.92%) |
| occurrences (all) | 72 | 10 | 35 |
| Constipation | | | |
| subjects affected / exposed | 61 / 572 (10.66%) | 12 / 182 (6.59%) | 34 / 574 (5.92%) |
| occurrences (all) | 72 | 13 | 34 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 34 / 572 (5.94%) | 7 / 182 (3.85%) | 13 / 574 (2.26%) |
| occurrences (all) | 45 | 8 | 15 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 35 / 572 (6.12%) | 3 / 182 (1.65%) | 30 / 574 (5.23%) |
| occurrences (all) | 45 | 5 | 33 |
| Pain in extremity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 40 / 572 (6.99%) | 11 / 182 (6.04%) | 27 / 574 (4.70%) |
| occurrences (all) | 48 | 12 | 28 |
| Back pain | | | |
| subjects affected / exposed | 89 / 572 (15.56%) | 29 / 182 (15.93%) | 66 / 574 (11.50%) |
| occurrences (all) | 128 | 33 | 69 |
| Arthralgia | | | |
| subjects affected / exposed | 147 / 572 (25.70%) | 19 / 182 (10.44%) | 79 / 574 (13.76%) |
| occurrences (all) | 214 | 25 | 99 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 29 / 572 (5.07%) | 18 / 182 (9.89%) | 0 / 574 (0.00%) |
| occurrences (all) | 30 | 20 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 55 / 572 (9.62%) | 14 / 182 (7.69%) | 33 / 574 (5.75%) |
| occurrences (all) | 74 | 22 | 39 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 43 / 572 (7.52%) | 15 / 182 (8.24%) | 18 / 574 (3.14%) |
| occurrences (all) | 46 | 17 | 20 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 02 June 2016 | The changes included: ● Added 2 exclusion criteria to o exclude patients who had not received bisphosphonates or denosumab at a stable dose (unless diagnosed with osteoporosis) and o exclude patients who had shown a hypersensitivity reaction to any of the study capsule components. ● Revised test drug information to remove information related to tablet formulations and add information related to the capsule formulation of study drug and placebo (chemical name, physical description and storage requirements). |
| 14 December 2017 | The changes included: ● Revised the number of events required for the primary endpoint to reflect that primary analysis was to occur when 262 rPD events were confirmed by independent central imaging review. All secondary endpoints were to be evaluated at the time of primary analysis (and are considered final, except for OS [Section 5.5.5]). ● Specified a step-wise approach for the statistical testing of the key secondary endpoints. To maintain the family-wise 2-sided type I error rate at 0.05, a parallel testing strategy between OS (with allocated type I error rate 0.04) and the other 4 endpoints (with allocated type I error rate 0.01) was developed. If the interim results of the OS analysis were statistically significant, no further analysis of OS would be completed. ● Specified that unblinding of study treatment assignment could have been performed if a patient discontinued due to disease progression and in the investigator's opinion this information was necessary to determine the next course of therapy. |
| 10 December 2018 | The changes included: ● Added an open-label extension period. Following unblinding at the end of the doubleblind period and demonstration of a statistically significant advantage of enzalutamide over placebo when added to ADT, as assessed by the primary endpoint, all eligible patients could be treated on study with open-label enzalutamide at the discretion of the patient and investigator. ● Specific QoL assessments related to deterioration of urinary symptoms and QoL were added to the secondary endpoints. |
| 31 March 2021 | The Changes included: ● Survival follow-up is considered complete and patients will be discontinued from long term follow-up when a final number of OS events has been reached. Sites will no longer be required to collect assessments at that time. ● Following the final OS analysis, patients continuing to receive clinical benefit from enzalutamide treatment may continue open-label treatment in another Astellas-sponsored study, provided they have not met any discontinuation criteria. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/31329516