# Clinical trial results:
# A phase III randomized, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)

## Summary

| | |
|---|---|
| EudraCT number | 2013-003438-33 |
| Trial protocol | IT ES FI SE DE BE GB NL NO PL FR |
| Global end of trial date | |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 28 February 2019 |
| First version publication date | 28 February 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | BAY88-8223/15396 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02043678 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Interim |
| Date of interim/final analysis | 15 February 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 February 2018 |
| 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 compare, in subjects with asymptomatic or mildly symptomatic chemotherapy-naïve bone-predominant metastatic CRPC, the clinical benefit of radium-223 dichloride versus placebo in combination with abiraterone and prednisone/prednisolone.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 30 March 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 7 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 55 |
| Country: Number of subjects enrolled | Belgium: 7 |
| Country: Number of subjects enrolled | Canada: 51 |
| Country: Number of subjects enrolled | Germany: 25 |
| Country: Number of subjects enrolled | Spain: 72 |
| Country: Number of subjects enrolled | Finland: 14 |
| Country: Number of subjects enrolled | France: 29 |
| Country: Number of subjects enrolled | United Kingdom: 64 |
| Country: Number of subjects enrolled | Italy: 52 |
| Country: Number of subjects enrolled | Netherlands: 5 |
| Country: Number of subjects enrolled | Norway: 8 |
| Country: Number of subjects enrolled | Sweden: 13 |
| Country: Number of subjects enrolled | United States: 90 |
| Country: Number of subjects enrolled | Israel: 59 |
| Country: Number of subjects enrolled | Japan: 114 |
| Country: Number of subjects enrolled | Singapore: 40 |

| | |
|---|---|
| Country: Number of subjects enrolled | Brazil: 51 |
| Country: Number of subjects enrolled | Poland: 28 |
| Country: Number of subjects enrolled | Russian Federation: 29 |
| Worldwide total number of subjects | 806 |
| EEA total number of subjects | 317 |

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) | 167 |
| From 65 to 84 years | 601 |
| 85 years and over | 38 |

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at multiple centers in 19 countries between 30 March 2014 (first subject first visit) and 15 February 2018 (data cut-off date).

### Pre-assignment

Screening details:

Overall, 1144 subjects were screened. Of them, 338 subjects did not complete screening, 806 subjects were randomized to treatment and 786 subjects received study treatment.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst, Carer, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Radium-223 dichloride + Abi/Pred |

Arm description:

Subjects received 6 intravenous (IV) administrations of radium-223 dichloride 50 kiloBecquerel per kilogram (kBq/kg) (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight at intervals of 4 weeks, along with oral abiraterone acetate tablets 1000 milligrams (mg) every day plus prednisone/prednisolone 5 mg twice daily (abi/pred) for 6 cycles, followed by abi/pred until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

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

Dosage and administration details:

Subjects received abiraterone acetate tablets 1000 milligrams (mg) every day until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

| | |
|---|---|
| Investigational medicinal product name | Prednisone/prednisolone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received 5 mg prednisone/prednisolone twice daily until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

| | |
|---|---|
| Investigational medicinal product name | Radium-223 dichloride |
| Investigational medicinal product code | BAY88-8223 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received 6 IV administrations of radium-223 dichloride 50 kiloBecquerel per kilogram (kBq/kg) (55 kBq/kg after implementation of NIST update) at intervals of 4 weeks.

| | |
|---|---|
| **Arm title** | Placebo + Abi/Pred |

Arm description:

Subjects received 6 IV administrations of placebo matched to radium-223 dichloride at intervals of 4 weeks, along with abi/pred for 6 cycles, followed by abi/pred until an on-study SSE occurred (or other withdrawal criteria were met).

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Abiraterone acetate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received abiraterone acetate tablets 1000 milligrams (mg) every day until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

| | |
|---|---|
| Investigational medicinal product name | Prednisone/prednisolone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received 5 mg prednisone/prednisolone twice daily until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

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

Dosage and administration details:

Subjects received 6 IV administrations of placebo matched to radium-223 dichloride at intervals of 4 weeks.

| **Number of subjects in period 1** | Radium-223 dichloride + Abi/Pred | Placebo + Abi/Pred |
|---|---|---|
| Started | 401 | 405 |
| Treated | 390 | 396 |
| Completed | 0 | 0 |
| Not completed | 401 | 405 |
| Consent withdrawn by subject | 10 | 13 |
| Ongoing with treatment | 87 | 104 |
| AE without clinical PD | 41 | 31 |
| Unspecified | 15 | 8 |
| AE with clinical progressive disease (PD) | 17 | 15 |
| Clinical PD | 88 | 112 |
| Radiological PD | 78 | 67 |
| Never treated | 11 | 9 |
| Lost to follow-up | 1 | 1 |
| Protocol-driven decision point | 53 | 45 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Radium-223 dichloride + Abi/Pred |
| Reporting group description: | |
| Subjects received 6 intravenous (IV) administrations of radium-223 dichloride 50 kiloBecquerel per kilogram (kBq/kg) (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight at intervals of 4 weeks, along with oral abiraterone acetate tablets 1000 milligrams (mg) every day plus prednisone/prednisolone 5 mg twice daily (abi/pred) for 6 cycles, followed by abi/pred until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met). | |
| Reporting group title | Placebo + Abi/Pred |
| Reporting group description: | |
| Subjects received 6 IV administrations of placebo matched to radium-223 dichloride at intervals of 4 weeks, along with abi/pred for 6 cycles, followed by abi/pred until an on-study SSE occurred (or other withdrawal criteria were met). | |

| Reporting group values | Radium-223 dichloride + Abi/Pred | Placebo + Abi/Pred | Total |
|---|---|---|---|
| Number of subjects | 401 | 405 | 806 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 70.9 | 71.4 | |
| standard deviation | ± 8.5 | ± 8.4 | - |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 401 | 405 | 806 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 2 |
| Asian | 79 | 78 | 157 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 10 | 16 | 26 |
| White | 285 | 284 | 569 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 26 | 26 | 52 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 17 | 23 | 40 |
| Not Hispanic or Latino | 361 | 355 | 716 |
| Unknown or Not Reported | 23 | 27 | 50 |
| Stage of prostate cancer at diagnosis (Tumor Node Metastasis [TNM] Classification) | | | |
| TNM staging system stands for Tumour, Node, Metastasis. Stage I: cancer is in half of one side of the prostate or less. Stage II: cancer is in more than half of one side of the prostate, completely contained within the prostate gland. Stage III: cancer has broken through the capsule of the prostate gland, and | | | |

| | | | |
|---|---|---|---|
| may have spread into tubes that carry semen. Stage IV: cancer has spread into nearby body organs, such as the back passage or bladder; or has spread to nearby lymph nodes; or has spread to other parts of the body outside the pelvis, such as the lungs or liver. | | | |
| Units: Subjects | | | |
| Missing | 19 | 24 | 43 |
| Stage I | 27 | 18 | 45 |
| Stage IIA | 22 | 20 | 42 |
| Stage IIB | 34 | 49 | 83 |
| Stage III | 102 | 88 | 190 |
| Stage IV | 197 | 206 | 403 |
| Cancer pain assessment by Brief Pain Inventory-Short Form (BPI-SF) | | | |
| The BPI-SF is a short, self-administered questionnaire with 11 items designed to evaluate the intensity of, and the impairment caused by pain. Four items measure pain intensity (pain now, average pain, worst pain, and least pain) using 0 (“no pain”) to 10 (“pain as bad as you can imagine”) numeric rating scales, and 7 items measure the level of interference with function caused by pain (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) using 0 (no interference) to 10 (complete interference) rating scales. | | | |
| Units: Subjects | | | |
| Missing | 25 | 33 | 58 |
| Asymptomatic (Worst pain score = 0) | 195 | 198 | 393 |
| Mildly Symptomatic (Worst pain score 1 - 3) | 181 | 174 | 355 |
| Gleason score at diagnosis | | | |
| The Gleason score is an indication of prognosis based on prostate pathology. The total score ranges from 2 to 10 (ie: "1+1" to "5+5") with a higher score reflecting less-differentiated tumors with worse prognosis. The total score is a sum of two numbers which are based on the microscopic appearance of cells. The first number is the score based on the dominant, cell morphology (scored 1-5) and the second number is based on the highest grade of the non-dominant cell pattern (scored 1-5). | | | |
| Units: Subjects | | | |
| Missing | 15 | 18 | 33 |
| Less than (<) 8 | 140 | 154 | 294 |
| Greater than or equal to (>=) 8 | 246 | 233 | 479 |
| Eastern Cooperative Oncology Group (ECOG) Performance Status | | | |
| Eastern cooperative oncology group (ECOG) performance status: 0= Fully active, able to carry on all pre-disease performance without restriction; 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; 3= Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4= Completely disabled, cannot carry on any self-care, totally confined to bed or chair. | | | |
| Units: Subjects | | | |
| Missing | 2 | 3 | 5 |
| ECOG=0 | 262 | 281 | 543 |
| ECOG=1 | 137 | 121 | 258 |
| Extent of Disease | | | |
| Units: Subjects | | | |
| Normal or abnormal because of benign bone disease | 2 | 0 | 2 |
| < 6 metastases | 134 | 141 | 275 |
| 6-20 metastases | 175 | 181 | 356 |
| >20 lesions but not a superscan | 71 | 70 | 141 |
| Superscan | 19 | 13 | 32 |
| Weight | | | |
| Units: Kilograms (kg) | | | |
| arithmetic mean | 82.19 | 82.40 | |
| standard deviation | ± 16.75 | ± 16.01 | - |

| | | | |
|---|---|---|---|
| Prostate-specific antigen<br>Units: Micrograms per liter (ug/L) | | | |
| arithmetic mean | 92.39 | 92.33 | |
| standard deviation | ± 191.62 | ± 328.00 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Radium-223 dichloride + Abi/Pred |

Reporting group description:

Subjects received 6 intravenous (IV) administrations of radium-223 dichloride 50 kiloBecquerel per kilogram (kBq/kg) (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight at intervals of 4 weeks, along with oral abiraterone acetate tablets 1000 milligrams (mg) every day plus prednisone/prednisolone 5 mg twice daily (abi/pred) for 6 cycles, followed by abi/pred until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

| | |
|---|---|
| Reporting group title | Placebo + Abi/Pred |

Reporting group description:

Subjects received 6 IV administrations of placebo matched to radium-223 dichloride at intervals of 4 weeks, along with abi/pred for 6 cycles, followed by abi/pred until an on-study SSE occurred (or other withdrawal criteria were met).

| | |
|---|---|
| Subject analysis set title | Intent-to-treat analysis set (ITT) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Included all randomized subjects.

| | |
|---|---|
| Subject analysis set title | Safety analysis set (SAF) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Included all randomized subjects who received at least one dose of any study drug.

### Primary: Symptomatic Skeletal Event Free Survival (SSE-FS)

| | |
|---|---|
| End point title | Symptomatic Skeletal Event Free Survival (SSE-FS) |

End point description:

SSE-FS was defined as time (months) from randomization to the earliest of onset date of skeletal symptoms treated with external beam radiotherapy (EBRT), onset date of pathological bone fracture, onset date of spinal cord compression, procedure date of tumor-related orthopedic surgery, or death from any cause. Subjects who died without prior SSE and ≥ 13 weeks after the last SSE assessment are censored at the last SSE assessment date. Subjects alive at the survival cut-off date are censored at the last date known to be alive. Subjects with multiple events are only counted for the category in which the first event occurred. If multiple SSE (component events) occur on the same date for 1 subject, the subject is only counted into 1 category in the order of: spinal cord compression > bone fracture > orthopedic surgery > EBRT.

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

End point timeframe:

From randomization until first onset of on-study symptomatic skeletal event (SSE) or death, up to 47 months

| End point values | Radium-223 dichloride + Abi/Pred | Placebo + Abi/Pred | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 401[1] | 405[2] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 22.3 (20.4 to 24.8) | 26.0 (21.8 to 28.3) | | |

Notes:
[1] - ITT
[2] - ITT

### Statistical analyses

| **Statistical analysis title** | Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred |
|---|---|
| Comparison groups | Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred |
| Number of subjects included in analysis | 806 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2636 |
| Method | Cox Proportional Hazards Model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.122 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.917 |
| upper limit | 1.374 |

## Secondary: Overall Survival (OS)

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

End point description:

OS was defined as the time (months) from the date of randomization to the date of death due to any cause. Subjects alive at the survival cut-off date were censored at the last date known to be alive. In the below table, "99999" indicates that upper limit cannot be estimated due to censored data.

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

End point timeframe:

From randomization until death from any cause, up to 47 months

| **End point values** | Radium-223 dichloride + Abi/Pred | Placebo + Abi/Pred | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 401[3] | 405[4] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 30.7 (25.8 to 99999) | 33.3 (30.2 to 41.1) | | |

Notes:
[3] - ITT
[4] - ITT

### Statistical analyses

| Statistical analysis title | Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred |
|---|---|
| Comparison groups | Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred |
| Number of subjects included in analysis | 806 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.128 |
| Method | Cox Proportional Hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.195 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.505 |

## Secondary: Radiological Progression Free Survival (rPFS)

| End point title | Radiological Progression Free Survival (rPFS) |
|---|---|

End point description:

rPFS was defined as the time (months) from the date of randomization to the date of confirmed radiological progression or death (if death occurred before progression) based on independent assessment.

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

End point timeframe:

From randomization until the date of confirmed radiological progression or death, up to 47 months

| End point values | Radium-223 dichloride + Abi/Pred | Placebo + Abi/Pred | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 401[5] | 405[6] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.2 (9.1 to 11.8) | 12.4 (10.8 to 14.5) | | |

Notes:

[5] - ITT

[6] - ITT

### Statistical analyses

| Statistical analysis title | Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred |
|---|---|
| Comparison groups | Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred |
| Number of subjects included in analysis | 806 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1283 |
| Method | Cox Proportional Hazards Model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.152 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 1.383 |

## Secondary: Time to Pain Progression

| End point title | Time to Pain Progression |
|---|---|

End point description:

Time to pain progression was defined as the interval from randomization to the first date a subject experienced pain progression, assessed by BPI-SF (see Baseline Characteristics) and defined as: an increase of 2 or more points in the average worst pain score (WPS) from baseline observed at 2 consecutive evaluations >= 4 weeks apart or initiation of short- or long-acting opioid use for pain for subjects with WPS 0 at baseline; an increase of 2 or more points in the average WPS from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart and an average WPS of ≥ 4 OR initiation of short- or long-acting opioid use for pain for subjects with WPS 1 to 3 at baseline. Subjects without pain progression at the end of study are censored at the last date known to have not progressed: the last evaluation date for pain scores or last visit when recorded opiate use, whichever is last. Subjects with no on-study assessment or no baseline assessment are censored at the date of randomization.

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

End point timeframe:

From randomization until the date of pain progression based on pain score, up to 47 months

| **End point values** | Radium-223 dichloride + Abi/Pred | Placebo + Abi/Pred | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 401[7] | 405[8] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 14.4 (11.1 to 20.1) | 18.7 (15.4 to 23.1) | | |

Notes:

[7] - ITT

[8] - ITT

### Statistical analyses

| **Statistical analysis title** | Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred |
|---|---|
| Comparison groups | Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred |
| Number of subjects included in analysis | 806 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1669 |
| Method | Cox Proportional Hazards Model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.145 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.945 |
| upper limit | 1.389 |

## Secondary: Time to Cytotoxic Chemotherapy

| | |
|---|---|
| End point title | Time to Cytotoxic Chemotherapy |

End point description:

Time to cytotoxic chemotherapy is time (months) from randomization to the earliest date of the first cytotoxic chemotherapy. Subjects who have not started cytotoxic chemotherapy during the study were censored at the last assessment date. In the below table, "99999" indicates that upper limit cannot be estimated due to censored data.

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

End point timeframe:

From randomization until the date of first cytotoxic chemotherapy, up to 47 months

| End point values | Radium-223 dichloride + Abi/Pred | Placebo + Abi/Pred | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 401[9] | 405[10] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 29.5 (26.5 to 35.7) | 28.5 (23.7 to 99999) | | |

Notes:

[9] - ITT

[10] - ITT

### Statistical analyses

| Statistical analysis title | Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred |
|---|---|
| Comparison groups | Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred |
| Number of subjects included in analysis | 806 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7871 |
| Method | Cox Proportional Hazards Model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.033 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.816 |
| upper limit | 1.308 |

## Secondary: Time to Opiate Use for Cancer Pain

| End point title | Time to Opiate Use for Cancer Pain |
|---|---|

End point description:

Time to opiate use for cancer pain was defined as the interval from the date of randomization to the date of opiate use.

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

End point timeframe:

From randomization until the date of opiate use, up to 47 months

| **End point values** | Radium-223 dichloride + Abi/Pred | Placebo + Abi/Pred | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 398[11] | 392[12] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 19.0 (14.4 to 23.2) | 22.6 (18.0 to 25.7) | | |

Notes:

[11] - ITT set excluding subjects who had opiate use at baseline

[12] - ITT set excluding subjects who had opiate use at baseline

### Statistical analyses

| **Statistical analysis title** | Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred |
|---|---|
| Comparison groups | Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred |
| Number of subjects included in analysis | 790 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2467 |
| Method | Cox Proportional Hazards Model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.126 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.921 |
| upper limit | 1.378 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From start of study treatment until the end of the treatment period, up to 47 months | |
| Assessment type | Non-systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Placebo + Abi/Pred |
| Reporting group description: | |
| Subjects received 6 IV administrations of placebo matched to radium-223 dichloride at intervals of 4 weeks, along with abi/pred for 6 cycles, followed by abi/pred until an on-study SSE occurred (or other withdrawal criteria were met). | |
| Reporting group title | Radium-223 dichloride + Abi/Pred |
| Reporting group description: | |
| Subjects received 6 intravenous (IV) administrations of radium-223 dichloride 50 kiloBecquerel per kilogram (kBq/kg) (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight at intervals of 4 weeks, along with oral abiraterone acetate tablets 1000 milligrams (mg) every day plus prednisone/prednisolone 5 mg twice daily (abi/pred) for 6 cycles, followed by abi/pred until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met). | |

| Serious adverse events | Placebo + Abi/Pred | Radium-223 dichloride + Abi/Pred | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 155 / 394 (39.34%) | 160 / 392 (40.82%) | |
| number of deaths (all causes) | 140 | 151 | |
| number of deaths resulting from adverse events | 20 | 26 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| B-cell lymphoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 5 / 394 (1.27%) | 3 / 392 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer recurrent | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bowen's disease | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Cholangiocarcinoma | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kaposi's sarcoma | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal sinus cancer | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 7 / 394 (1.78%) | 6 / 392 (1.53%) | |
| occurrences causally related to treatment / all | 0 / 20 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid cancer metastatic | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Brain neoplasm | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal cancer | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Vascular disorders** | | | |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 394 (0.51%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 5 / 392 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 8 / 394 (2.03%) | 9 / 392 (2.30%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 12 | |
| deaths causally related to treatment / all | 7 / 7 | 6 / 6 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatism | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 394 (1.02%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pneumonitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 5 / 392 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Lower respiratory tract inflammation | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase | | | |

| | | | |
|---|---|---|---|
| increased | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Femur fracture | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax traumatic | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue injury | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulna fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic fracture | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 11 / 392 (2.81%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 18 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain contusion | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 4 / 394 (1.02%) | 4 / 392 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Atrial fibrillation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 394 (1.78%) | 4 / 392 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary ostial stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorder | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Nervous system disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cauda equina syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Monoplegia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 8 / 394 (2.03%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient global amnesia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal epidural haematoma | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cognitive disorder | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parkinson's disease | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial neuralgia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nerve root compression | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 7 / 392 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 2 | 4 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphopenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 394 (1.27%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal achalasia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal perforation | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 3 / 392 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disease | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 5 / 392 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 394 (1.02%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary bladder haemorrhage | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 4 / 392 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Primary adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 10 / 394 (2.54%) | 8 / 392 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 5 / 394 (1.27%) | 4 / 392 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 3 / 392 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 8 / 392 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 3 | 5 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 6 / 392 (1.53%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal osteoarthritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 394 (0.51%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious colitis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 394 (0.00%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lyme disease | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 10 / 394 (2.54%) | 8 / 392 (2.04%) | |
| occurrences causally related to treatment / all | 1 / 14 | 0 / 9 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 2 / 2 | 2 / 2 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 394 (1.02%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 394 (2.28%) | 14 / 392 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Urosepsis | | | |
| subjects affected / exposed | 7 / 394 (1.78%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis fungal | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 4 / 392 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 2 / 392 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 392 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 392 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo + Abi/Pred | Radium-223 dichloride + Abi/Pred | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 366 / 394 (92.89%) | 360 / 392 (91.84%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 78 / 394 (19.80%) | 58 / 392 (14.80%) | |
| occurrences (all) | 191 | 155 | |
| Hot flush | | | |
| subjects affected / exposed | 49 / 394 (12.44%) | 23 / 392 (5.87%) | |
| occurrences (all) | 51 | 25 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 40 / 394 (10.15%) | 34 / 392 (8.67%) | |
| occurrences (all) | 54 | 44 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 60 / 394 (15.23%) | 51 / 392 (13.01%) | |
| occurrences (all) | 69 | 64 | |
| Fatigue | | | |
| subjects affected / exposed | 79 / 394 (20.05%) | 89 / 392 (22.70%) | |
| occurrences (all) | 109 | 119 | |
| Pyrexia | | | |
| subjects affected / exposed | 27 / 394 (6.85%) | 24 / 392 (6.12%) | |
| occurrences (all) | 38 | 29 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 35 / 394 (8.88%) | 33 / 392 (8.42%) | |
| occurrences (all) | 41 | 37 | |
| Dyspnoea | | | |
| subjects affected / exposed | 26 / 394 (6.60%) | 17 / 392 (4.34%) | |
| occurrences (all) | 27 | 21 | |
| Psychiatric disorders | | | |
| Insomnia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 22 / 394 (5.58%) | 25 / 392 (6.38%) | |
| occurrences (all) | 23 | 28 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 59 / 394 (14.97%) | 68 / 392 (17.35%) | |
| occurrences (all) | 145 | 176 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 53 / 394 (13.45%) | 60 / 392 (15.31%) | |
| occurrences (all) | 102 | 124 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 38 / 394 (9.64%) | 55 / 392 (14.03%) | |
| occurrences (all) | 49 | 76 | |
| Traumatic fracture | | | |
| subjects affected / exposed | 14 / 394 (3.55%) | 37 / 392 (9.44%) | |
| occurrences (all) | 31 | 63 | |
| Contusion | | | |
| subjects affected / exposed | 26 / 394 (6.60%) | 24 / 392 (6.12%) | |
| occurrences (all) | 32 | 30 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 30 / 394 (7.61%) | 38 / 392 (9.69%) | |
| occurrences (all) | 35 | 44 | |
| Headache | | | |
| subjects affected / exposed | 27 / 394 (6.85%) | 28 / 392 (7.14%) | |
| occurrences (all) | 35 | 42 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 45 / 394 (11.42%) | 54 / 392 (13.78%) | |
| occurrences (all) | 80 | 112 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 72 / 394 (18.27%) | 56 / 392 (14.29%) | |
| occurrences (all) | 86 | 64 | |
| Abdominal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 12 / 394 (3.05%) | 22 / 392 (5.61%) | |
| occurrences (all) | 14 | 23 | |
| Diarrhoea | | | |
| subjects affected / exposed | 57 / 394 (14.47%) | 64 / 392 (16.33%) | |
| occurrences (all) | 82 | 101 | |
| Dyspepsia | | | |
| subjects affected / exposed | 15 / 394 (3.81%) | 20 / 392 (5.10%) | |
| occurrences (all) | 15 | 22 | |
| Nausea | | | |
| subjects affected / exposed | 59 / 394 (14.97%) | 66 / 392 (16.84%) | |
| occurrences (all) | 64 | 80 | |
| Vomiting | | | |
| subjects affected / exposed | 31 / 394 (7.87%) | 37 / 392 (9.44%) | |
| occurrences (all) | 34 | 45 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 15 / 394 (3.81%) | 25 / 392 (6.38%) | |
| occurrences (all) | 20 | 36 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 75 / 394 (19.04%) | 79 / 392 (20.15%) | |
| occurrences (all) | 128 | 111 | |
| Bone pain | | | |
| subjects affected / exposed | 52 / 394 (13.20%) | 47 / 392 (11.99%) | |
| occurrences (all) | 68 | 65 | |
| Back pain | | | |
| subjects affected / exposed | 119 / 394 (30.20%) | 133 / 392 (33.93%) | |
| occurrences (all) | 170 | 219 | |
| Muscle spasms | | | |
| subjects affected / exposed | 28 / 394 (7.11%) | 25 / 392 (6.38%) | |
| occurrences (all) | 31 | 30 | |
| Muscular weakness | | | |
| subjects affected / exposed | 28 / 394 (7.11%) | 24 / 392 (6.12%) | |
| occurrences (all) | 36 | 38 | |
| Musculoskeletal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 43 / 394 (10.91%) | 40 / 392 (10.20%) | |
| occurrences (all) | 53 | 47 | |
| Myalgia | | | |
| subjects affected / exposed | 21 / 394 (5.33%) | 22 / 392 (5.61%) | |
| occurrences (all) | 24 | 27 | |
| Neck pain | | | |
| subjects affected / exposed | 21 / 394 (5.33%) | 16 / 392 (4.08%) | |
| occurrences (all) | 24 | 17 | |
| Osteoporosis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 23 / 392 (5.87%) | |
| occurrences (all) | 1 | 23 | |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 23 / 392 (5.87%) | |
| occurrences (all) | 1 | 58 | |
| Pain in extremity | | | |
| subjects affected / exposed | 50 / 394 (12.69%) | 45 / 392 (11.48%) | |
| occurrences (all) | 67 | 61 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 25 / 394 (6.35%) | 26 / 392 (6.63%) | |
| occurrences (all) | 29 | 35 | |
| Pathological fracture | | | |
| subjects affected / exposed | 14 / 394 (3.55%) | 33 / 392 (8.42%) | |
| occurrences (all) | 24 | 47 | |
| Spinal pain | | | |
| subjects affected / exposed | 21 / 394 (5.33%) | 21 / 392 (5.36%) | |
| occurrences (all) | 24 | 24 | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 12 / 394 (3.05%) | 20 / 392 (5.10%) | |
| occurrences (all) | 18 | 21 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 29 / 394 (7.36%) | 23 / 392 (5.87%) | |
| occurrences (all) | 36 | 30 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 34 / 394 (8.63%) | 30 / 392 (7.65%) | |
| occurrences (all) | 48 | 37 | |

| | | | |
|---|---|---|---|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 26 / 394 (6.60%)<br>30 | 36 / 392 (9.18%)<br>49 | |
| Metabolism and nutrition disorders<br>Hypokalaemia<br>subjects affected / exposed<br>occurrences (all) | 39 / 394 (9.90%)<br>65 | 39 / 392 (9.95%)<br>62 | |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 38 / 394 (9.64%)<br>39 | 53 / 392 (13.52%)<br>66 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 August 2014 | Amendment 1 (integrated protocol Version 2.0) specified the following key modifications: 1. Modified the inclusion criterion to clarify the permitted age range. 2. Modified the inclusion criterion to expand the permitted estimated GFR. 3. Clarified study treatment is either radium-223 dichloride (Arm A) or placebo (Arm B). 4. Clarified the maximum radium-223 dichloride treatment duration. 7. Clarified that abiraterone is not considered study medication after an on-study SSE. 8. Clarified he process for maintaining the blind. 9. Corrected the hemoglobin level that must be met for dosing. 10. Added collection of SSEs during the screening period. 11. Clarified that survival status would be collected throughout the study. 12. Clarified that collection of cancer-related treatments includes androgen synthesis inhibitors/androgen receptor antagonists and excludes analgesics. 13. Added the modified RECIST v1.1 criteria. |
| 11 June 2015 | Amendment 2 (integrated protocol Version 3.0) specified the following key modifications: 1. Updated dosing and dose calibration of radium-223 dichloride to reflect revised NIST standardization for radium-223. 2. Removed cytological confirmation of adenocarcinoma of the prostate from inclusion criteria; histological confirmation only. 3. Clarified that the treatment period ended when a subject received abiraterone/prednisone as the standard of care (non-IMP) after an SSE. 4. Added an exclusion for immunotherapy (e.g., sipuleucel-T) within 4 weeks before the first dose of radium-223 dichloride. 5. Clarified duration of prohibited concomitant therapy was from screening onwards. 6. Clarified potassium requirement for ECG collection. |
| 12 September 2016 | Amendment 4 (integrated protocol Version 4.0) specified the following key modifications: 1. Clarified continuation of medical castration. 2. Clarified documentation of radiological progression. 3. Clarified study drug handling if administration was postponed more than 3 days. 4. Clarified treatment unblinding procedures. 5. Removed bisphosphonate timing requirements. |
| 02 April 2018 | Amendment 6 (integrated protocol Version 5.0) specified the following modifications: 1. Requested that bone fractures and bone-associated events (e.g., osteoporosis) were to be reported as (S)AEs, including during long-term follow-up, regardless of the investigator's causality assessment. 2. Added an independent radiological review of fractures. 3. Added that radium-223 dichloride should not be given in combination with abiraterone plus prednisone/prednisolone during follow-up. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Occurrence of "±" in relation with standard deviation is auto generated. Decimal places were automatically truncated if last decimals is equals to zero.

Notes: