# Clinical trial results:
# A Double-blind, Randomised, Multiple Dose, Phase III, Multicentre Study of Alpharadin in the Treatment of Patients With Symptomatic Hormone Refractory Prostate Cancer With Skeletal Metastases

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

| | |
|---|---|
| EudraCT number | 2007-006195-11 |
| Trial protocol | SE FR GB BE SK ES CZ NL IT DE |
| Global end of trial date | 13 February 2014 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 24 July 2016 |
| First version publication date | 30 July 2015 |
| Version creation reason | • Correction of full data set<br>NA |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | BAY88-8223/15245 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00699751 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Other: BC1-06 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany, |
| 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 | Final |
| Date of interim/final analysis | 13 February 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 13 February 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare, in subjects with symptomatic hormone refractory prostate cancer (HRPC) and skeletal metastases, the efficacy of best standard of care (BSoC) plus radium-223 dichloride versus BSoC plus placebo, with the primary efficacy endpoint being overall survival.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. 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.
The formal interim analysis (IA) was performed using the data cut-off date of 14 October 2010 when a total of 316 deaths had been observed; this resulted in the Independent data monitoring committee's (IDMC) recommendation to unblind the study, to stop further placebo treatment, and to offer radium-223 dichloride to placebo subjects who were still participating in the study (who had not withdrawn from the study) and who fulfilled the eligibility criteria as defined in amendment 6 to the Protocol BC1-06, as the primary efficacy analysis of overall survival had crossed the prespecified boundary for efficacy.

Background therapy:

BSoC was regarded as the routine standard of care at each center, for example local external beam radiation therapy (EBRT), corticosteroids, antiandrogens, estrogens (example: stilboestrol), estramustine or ketoconazole.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 12 June 2008 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Norway: 138 |
| Country: Number of subjects enrolled | Belgium: 10 |
| Country: Number of subjects enrolled | Australia: 30 |
| Country: Number of subjects enrolled | Brazil: 39 |
| Country: Number of subjects enrolled | Canada: 20 |
| Country: Number of subjects enrolled | Czech Republic: 52 |
| Country: Number of subjects enrolled | France: 14 |

| | |
|---|---|
| Country: Number of subjects enrolled | Germany: 56 |
| Country: Number of subjects enrolled | Hong Kong: 21 |
| Country: Number of subjects enrolled | Israel: 8 |
| Country: Number of subjects enrolled | Italy: 18 |
| Country: Number of subjects enrolled | Netherlands: 10 |
| Country: Number of subjects enrolled | Poland: 61 |
| Country: Number of subjects enrolled | Singapore: 5 |
| Country: Number of subjects enrolled | Slovakia: 22 |
| Country: Number of subjects enrolled | Spain: 46 |
| Country: Number of subjects enrolled | Sweden: 90 |
| Country: Number of subjects enrolled | United Kingdom: 258 |
| Country: Number of subjects enrolled | United States: 23 |
| Worldwide total number of subjects | 921 |
| EEA total number of subjects | 775 |

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) | 231 |
| From 65 to 84 years | 673 |
| 85 years and over | 17 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects with progressive symptomatic HRPC, with at least 2 skeletal metastases on bone scan and no known visceral metastases, could participate in the study.

### Pre-assignment

Screening details:

Subjects were to be randomized in a 2:1, a total of 921 subjects were enrolled in the study and were randomized to receive either Alpharadin [Radium-223 dichloride (Xofigo, BAY88-8223)] or placebo study treatment, which resulted in 614 subjects enrolled in the Alpharadin group and 307 enrolled in the placebo group.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Radium-223 dichloride (Xofigo, BAY88-8223) |

Arm description:

Radium-223 50 kiloBecquerel (kBq)/kilogram (kg) body weight for 6 IV administrations separated by 4 weeks intervals plus BSoC.

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

Dosage and administration details:

Radium-223 50 kBq/kg body weight for 6 IV administrations separated by 4 weeks intervals plus BSoC.

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

Arm description:

Isotonic saline for 6 intravenous (IV) administrations separated by 4 weeks intervals plus BSoC.

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

Isotonic saline for 6 IV administrations separated by 4 weeks intervals plus BSoC.

| Number of subjects in period 1 | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo |
|---|---|---|
| Started | 614 | 307 |
| Completed | 614 | 307 |

| Period 2 | |
|---|---|
| Period 2 title | Overall study |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

**Arms**

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Radium-223 Dichloride (Xofigo, BAY88-8223) |

Arm description:

Subjects received BSoC plus radium-223 50 kBq/kg body weight for 6 IV administrations separated by 4 weeks intervals.

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

Dosage and administration details:

Radium-223 50 kBq/kg body weight for 6 IV administrations separated by 4 weeks intervals plus BSoC.

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

Arm description:

Subjects received BSoC plus isotonic saline for 6 IV administrations separated by 4 weeks intervals.

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

Isotonic saline for 6 IV administrations separated by 4 weeks intervals plus BSoC.

| | |
|---|---|
| **Arm title** | Placebo Randomized, Then Switched to Radium-223 Dichloride |

Arm description:

Subjects received BSoC plus isotonic saline for 6 IV administrations separated by 4 weeks intervals from randomization to data cut-off date of 15 July 2011; subjects received radium-223 50 kBq/kg body weight for 6 intravenous administrations separated by 4 weeks intervals from 15 July 2011 to the end of study.

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

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

Dosage and administration details:

Radium-223 50 kBq/kg body weight for 6 IV administrations separated by 4 weeks intervals plus BSoC.

| | |
|---|---|
| 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:

Isotonic saline for 6 IV administrations separated by 4 weeks intervals plus BSoC.

| **Number of subjects in period 2** | Radium-223 Dichloride (Xofigo, BAY88-8223) | Placebo | Placebo Randomized, Then Switched to Radium-223 Dichloride |
|---|---|---|---|
| Started | 614 | 307 | 26 |
| Completed all 6 Injections | 389 | 145 | 17 |
| Entered 3-Year Follow-up Period | 407 | 168 | 15 [1] |
| Completed 3-Year Follow-up Period | 49 [2] | 12 [3] | 0 [4] |
| Completed | 389 | 145 | 17 |
| Not completed | 225 | 162 | 9 |
| Adverse Event | 97 | 63 | 4 |
| Investigator Request | 27 | 27 | 1 |
| Death | 28 | 29 | - |
| Unspecified | 30 | 20 | - |
| Subject Request | 43 | 23 | - |
| Treatment Completion Page not expected | - | - | 4 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Of subjects who completed treatment of all 6 injections, only a few subjects entered the 3-year follow-up period voluntarily. Hence, the number of subjects at this milestone seems inconsistent with the number of subjects in the arm.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Of subjects who started treatment, only a few subjects entered and completed the 3-year follow-up period voluntarily. Hence, the number of subjects at this milestone seems inconsistent with the number of subjects in the arm.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Of subjects who started treatment, only a few subjects entered and completed the 3-year follow-up period voluntarily. Hence, the number of subjects at this milestone seems inconsistent with

the number of subjects in the arm.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Of subjects who started treatment, only a few subjects entered and completed the 3-year follow-up period voluntarily. Hence, the number of subjects at this milestone seems inconsistent with the number of subjects in the arm.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Radium-223 dichloride (Xofigo, BAY88-8223) |
| Reporting group description: | |
| Radium-223 50 kiloBecquerel (kBq)/kilogram (kg) body weight for 6 IV administrations separated by 4 weeks intervals plus BSoC. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Isotonic saline for 6 intravenous (IV) administrations separated by 4 weeks intervals plus BSoC. | |

| Reporting group values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | Total |
|---|---|---|---|
| Number of subjects | 614 | 307 | 921 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: Years | | | |
| arithmetic mean | 70.2 | 70.8 | |
| standard deviation | ± 8.1 | ± 7.87 | - |
| Gender categorical<br>Units: Subjects | | | |
| Male | 614 | 307 | 921 |
| Total Alkaline Phosphatase (ALP) | | | |
| The total amount of ALP in the blood was determined at baseline. | | | |
| Units: Subjects | | | |
| < 220 Units/Liter (U/L) | 348 | 169 | 517 |
| >= 220 U/L | 266 | 138 | 404 |
| Current use of bisphosphonates | | | |
| Subjects may have been on bisphosphonate therapy during the study. | | | |
| Units: Subjects | | | |
| Yes | 250 | 124 | 374 |
| No | 364 | 183 | 547 |
| Any prior use of docetaxel<br>Units: Subjects | | | |
| Yes | 352 | 174 | 526 |
| No | 262 | 133 | 395 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Radium-223 dichloride (Xofigo, BAY88-8223) |
| Reporting group description: | |
| Radium-223 50 kiloBecquerel (kBq)/kilogram (kg) body weight for 6 IV administrations separated by 4 weeks intervals plus BSoC. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Isotonic saline for 6 intravenous (IV) administrations separated by 4 weeks intervals plus BSoC. | |
| Reporting group title | Radium-223 Dichloride (Xofigo, BAY88-8223) |
| Reporting group description: | |
| Subjects received BSoC plus radium-223 50 kBq/kg body weight for 6 IV administrations separated by 4 weeks intervals. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received BSoC plus isotonic saline for 6 IV administrations separated by 4 weeks intervals. | |
| Reporting group title | Placebo Randomized, Then Switched to Radium-223 Dichloride |
| Reporting group description: | |
| Subjects received BSoC plus isotonic saline for 6 IV administrations separated by 4 weeks intervals from randomization to data cut-off date of 15 July 2011; subjects received radium-223 50 kBq/kg body weight for 6 intravenous administrations separated by 4 weeks intervals from 15 July 2011 to the end of study. | |
| Subject analysis set title | Intent-to-treat (ITT) population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| ITT population (N=921) was defined as all randomized subjects. | |

### Primary: Overall Survival

| | |
|---|---|
| End point title | Overall Survival |
| End point description: | |
| Overall survival was defined as the time from date of randomization to the date of death. | |
| End point type | Primary |
| End point timeframe: | |
| From randomization to death due to any cause until the data cut-off date (15JUL2011) approximately 3 years after start of enrollment | |

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[1] | 307[2] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 14.9 (13.9 to 16.1) | 11.3 (10.1 to 12.8) | | |

Notes:

[1] - ITT population.

[2] - ITT population.

## Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of overall survival, and also for the secondary endpoints, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.
The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[3] |
| P-value | = 0.00005 [4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.691 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.578 |
| upper limit | 0.827 |

Notes:

[3] - Comparison with placebo

[4] - Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

## Secondary: Time to Total Alkaline Phosphatase (ALP) Progression

| End point title | Time to Total Alkaline Phosphatase (ALP) Progression |
|---|---|

End point description:

The time from the first study drug administration to when ALP progression was observed, defined as: 1) In subjects with no ALP decline from baseline; a greater than or equal to 25 percent (%) increase from baseline value and an increase in absolute value of greater than or equal to 2 nanogram (ng)/milliliter (mL), at least 12 weeks from baseline; 2) In subjects with initial ALP decline from baseline; the time from start of treatment to first ALP increase that was greater than or equal to 25% increase and at least 2 ng/mL above the nadir value, which was confirmed by a second value obtained 3 or more weeks later. '99999" indicates 95% confidence interval upper limit was not estimable due to insufficient number of subjects with events.

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

End point timeframe:

From randomization to first ALP progression until the data cut-off date (10 Oct 2014) approximately 3 years after start of enrollment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[5] | 307[6] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.4 (7.1 to 99999) | 3.8 (3.6 to 4.2) | | |

Notes:

[5] - The ITT population was all randomized subjects.

[6] - The ITT population was all randomized subjects.

## Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of time to total ALP progression, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.
The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[7] |
| P-value | < 0.00001 [8] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.169 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.131 |
| upper limit | 0.22 |

Notes:

[7] - Comparison with placebo

[8] - Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

## Secondary: Percentage of Subjects With Total ALP Response at Week 12

| End point title | Percentage of Subjects With Total ALP Response at Week 12 |
|---|---|

End point description:

ALP levels were measured in subjects' blood at Week 12 and compared to baseline values. A confirmed total ALP response (either >=30% or 50% reduction from baseline) was confirmed by a second total ALP value approximately 4 weeks later.

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

End point timeframe:

At Baseline and Week 12 based of 10 Oct 2014 cutoff date

| **End point values** | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 497[9] | 211[10] | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| >=30% reduction of ALP in blood level | 59.4 | 6.2 | | |

| | | | | |
|---|---|---|---|---|
| >=50% reduction of ALP in blood level | 32.6 | 1.4 | | |
| Confirmed Total ALP Response (>=30%) | 47.1 | 3.3 | | |
| Confirmed Total ALP Response (>=50%) | 27.4 | 0.9 | | |

Notes:

[9] - Subjects in the ITT population and had no missing values for this endpoint.

[10] - Subjects in the ITT population and had no missing values for this endpoint.

## Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of >=30% reduction in blood level, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 708 |
| Analysis specification | Pre-specified |
| Analysis type | other[11] |
| P-value | < 0.001 [12] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[11] - Comparison with placebo

[12] - Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.
>=30% reduction in blood level.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

The null hypothesis for the comparison of >=50% reduction in blood level, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 708 |
| Analysis specification | Pre-specified |
| Analysis type | other[13] |
| P-value | < 0.001 [14] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[13] - Comparison with placebo

[14] - Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel. >=50% reduction in blood level.

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

The null hypothesis for the comparison of Confirmed Total ALP Response (>=30%), was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 708 |
| Analysis specification | Pre-specified |
| Analysis type | other[15] |
| P-value | < 0.001 [16] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[15] - Comparison with placebo

[16] - Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel. Confirmed Total ALP Response (>=30%).

| **Statistical analysis title** | Statistical Analysis 4 |
|---|---|

Statistical analysis description:

The null hypothesis for the comparison of Confirmed Total ALP Response (>=50%), was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 708 |
| Analysis specification | Pre-specified |
| Analysis type | other[17] |
| P-value | < 0.001 [18] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[17] - Comparison with placebo

[18] - Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel. Confirmed Total ALP Response (>=50%).

## Secondary: Percentage of Subjects With Total ALP Response at End of Treatment (EOT; Week 24 or at the Time the Subject Dies or Discontinues Treatment Phase)

| | |
|---|---|
| End point title | Percentage of Subjects With Total ALP Response at End of Treatment (EOT; Week 24 or at the Time the Subject Dies or Discontinues Treatment Phase) |

End point description:

ALP levels were measured in subjects' blood at EOT (Week 24) and compared to baseline values. A confirmed total ALP response (>=50% reduction from baseline) was confirmed by a second total ALP value approximately 4 weeks later.

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

End point timeframe:

At Baseline and End of Treatment (Week 24 or at the time the subject dies or discontinues treatment phase) based on 10 Oct 2014 cutoff date

| **End point values** | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 589[19] | 288[20] | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| >=30% reduction of ALP in blood level | 59.9 | 4.5 | | |
| >=50% reduction of ALP in blood level | 34.6 | 1.7 | | |
| Confirmed Total ALP Response (>=50%) | 13.9 | 1 | | |

Notes:

[19] - Subjects in the ITT population and had no missing values for this endpoint

[20] - Subjects in the ITT population and had no missing values for this endpoint

## Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of >=30% reduction in blood level, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 877 |
| Analysis specification | Pre-specified |
| Analysis type | other[21] |
| P-value | < 0.001 [22] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[21] - Comparison with placebo

[22] - >=30% reduction in blood level. Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior
use of Docetaxel.

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

The null hypothesis for the comparison of Confirmed Total ALP Response (>=50%), was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 877 |
| Analysis specification | Pre-specified |
| Analysis type | other[23] |
| P-value | < 0.001 [24] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[23] - Comparison with placebo

[24] - Confirmed Total ALP Response (>=50%). Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

The null hypothesis for the comparison of >=50% reduction in blood level, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 877 |
| Analysis specification | Pre-specified |
| Analysis type | other[25] |
| P-value | < 0.001 [26] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[25] - Comparison with placebo

[26] - >=50% reduction in blood level. Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

## Secondary: Percentage of Subjects With Total ALP Normalization at Week 12

| End point title | Percentage of Subjects With Total ALP Normalization at Week 12 |
|---|---|

End point description:

The return of total ALP value to within normal range at 12 weeks in 2 consecutive measurements (at least 2 weeks apart) after start of treatment in subjects who had ALP above the upper limit of normal (ULN) at baseline.

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

End point timeframe:

At Baseline and Week 12

| **End point values** | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 321[27] | 140[28] | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 34 | 1.4 | | |

Notes:

[27] - Subjects in the ITT population and had no missing values for this endpoint.

[28] - Subjects in the ITT population and had no missing values for this endpoint.

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Total ALP normalization, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
|---|---|
| Number of subjects included in analysis | 461 |
| Analysis specification | Pre-specified |
| Analysis type | other[29] |
| P-value | < 0.001 [30] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[29] - comparison with placebo

[30] - Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.
Total ALP normalization.

## Secondary: Percentage Change From Baseline in Total ALP at Week 12

| End point title | Percentage Change From Baseline in Total ALP at Week 12 |
|---|---|

End point description:

ALP level was measured in subject's blood at Week 12 and the percent change from the baseline value was calculated (ALP level at week 12 minus ALP level at baseline)/(ALP level at baseline)*100.

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

End point timeframe:

At Baseline and Week 12

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 497[31] | 211[32] | | |
| Units: Percentage change | | | | |
| least squares mean (standard error) | -32.2 (± 1.8) | 37.2 (± 2.77) | | |

Notes:

[31] - Subjects in the ITT population and had no missing values for this endpoint

[32] - Subjects in the ITT population and had no missing values for this endpoint

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Percentage change from baseline, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 708 |
| Analysis specification | Pre-specified |
| Analysis type | other[33] |
| P-value | < 0.001 [34] |
| Method | ANCOVA |

Notes:

[33] - comparison with placebo

[34] - Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.
Percentage change from Baseline.

## Secondary: Maximum Percentage Decrease From Baseline in Total ALP up to Week 12

| End point title | Maximum Percentage Decrease From Baseline in Total ALP up to Week 12 |
|---|---|

End point description:

ALP level was measured in subject's blood up to week 12 and the maximum percent decrease from the baseline up to Week 12 value was calculated as the minimum value of [(ALP level up to week 12 minus ALP level at baseline)/(ALP level at baseline)*100] by subject, and set to zero if no decrease from baseline.

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

End point timeframe:

From baseline to Week 12

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 582[35] | 284[36] | | |
| Units: Percentage change | | | | |
| least squares mean (standard error) | -38.9 (± 0.76) | -5.9 (± 1.09) | | |

Notes:

[35] - Subjects in the ITT population and had no missing values for this endpoint

[36] - Subjects in the ITT population and had no missing values for this endpoint

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Maximum Percentage decrease from baseline to week 12, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
|---|---|
| Number of subjects included in analysis | 866 |
| Analysis specification | Pre-specified |
| Analysis type | other[37] |
| P-value | < 0.001 [38] |
| Method | ANCOVA |

Notes:

[37] - Comparison with placebo

[38] - Maximum percentage decrease from baseline to week 12.
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

### Secondary: Percentage Change From Baseline in Total ALP at EOT (Week 24 or at the Time the Subject Dies or Discontinues Treatment Phase)

| End point title | Percentage Change From Baseline in Total ALP at EOT (Week 24 or at the Time the Subject Dies or Discontinues Treatment Phase) |
|---|---|

End point description:

ALP level was measured in subject's blood at EOT (Week 24) and the percent change from the baseline value was calculated (ALP level at EOT minus ALP level at baseline)/(ALP level at baseline)*100.

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

End point timeframe:

At Baseline and End of Treatment (Week 24 or at the time the subject dies or discontinues treatment phase) based on 10 Oct 2014 cutoff date

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 589[39] | 288[40] | | |
| Units: Percent change | | | | |
| least squares mean (standard error) | -29.9 (± 3.13) | 62.1 (± 4.48) | | |

Notes:

[39] - Subjects in the ITT population and had no missing values for this endpoint.

[40] - Subjects in the ITT population and had no missing values for this endpoint.

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Percentage change from baseline, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 877 |
| Analysis specification | Pre-specified |
| Analysis type | other[41] |
| P-value | < 0.001 [42] |
| Method | ANCOVA |

Notes:

[41] - Comparison with placebo.

[42] - Percentage change from baseline.
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

## Secondary: Maximum Percentage Decrease From Baseline in Total ALP During the 24 Week Treatment

| End point title | Maximum Percentage Decrease From Baseline in Total ALP During the 24 Week Treatment |
|---|---|

End point description:

ALP level was measured in subject's blood during the 24 week treatment (up to EOT) and the maximum percent decrease from baseline during the 24 week treatment value was calculated as the minimum value of [(ALP level up to week 24 minus ALP level at baseline)/(ALP level at baseline)*100] by subject, and set to zero if no decrease from baseline.

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

End point timeframe:

From baseline During the 24 Week Treatment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 589[43] | 288[44] | | |
| Units: Percentage change | | | | |
| least squares mean (standard error) | -44.4 (± 0.8) | -7.5 (± 1.14) | | |

Notes:

[43] - Subjects in the ITT population and had no missing values for this endpoint

[44] - Subjects in the ITT population and had no missing values for this endpoint

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Maximum Percentage decrease from baseline during the 24 week treatment, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 877 |
| Analysis specification | Pre-specified |
| Analysis type | other[45] |
| P-value | < 0.001 [46] |
| Method | ANCOVA |

Notes:

[45] - Comparison with placebo

[46] - Maximum Percentage decrease from baseline.
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

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

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

End point description:

The time from the first study drug administration to when PSA progression was observed, defined as: 1) In subjects with no PSA decline from baseline; a greater than or equal to 25% increase from baseline value and an increase in absolute value of greater than or equal to 2 ng/mL, at least 12 weeks from baseline; 2) In subjects with initial PSA decline from baseline; the time from start of treatment to first PSA increase that was greater than or equal to 25% increase and at least 2 ng/mL above the nadir value, which was confirmed by a second value obtained 3 or more weeks later.

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

End point timeframe:

From randomization to first PSA progression until the data cut-off date (10 Oct 2014) approximately 3 years after start of enrollment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[47] | 307[48] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 3.6 (3.5 to 3.8) | 3.4 (3.3 to 3.5) | | |

Notes:

[47] - The ITT population was all randomized subjects

[48] - The ITT population was all randomized subjects

## Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Time to PSA progression, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists. The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[49] |
| P-value | < 0.00001 [50] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.643 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.539 |
| upper limit | 0.768 |

Notes:

[49] - Comparison with placebo

[50] - Time to PSA progression. Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

## Secondary: Percentage of Subjects With PSA Response at Week 12

| | |
|---|---|
| End point title | Percentage of Subjects With PSA Response at Week 12 |

End point description:

PSA levels were measured in subjects' blood at Week 12 and compared to baseline values. A confirmed PSA response (>/=50% reduction from baseline) was confirmed by a second PSA value approximately 4 weeks later.

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

End point timeframe:

At Baseline and Week 12

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 493[51] | 210[52] | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| >=30% reduction of PSA in blood level | 16.4 | 6.2 | | |
| >=50% reduction of PSA in blood level | 7.7 | 4.3 | | |
| Confirmed PSA Response (>=50%) | 5.7 | 1.9 | | |

Notes:

[51] - Subjects in the ITT population and had no missing values for this endpoint

[52] - Subjects in the ITT population and had no missing values for this endpoint

## Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of >=30% reduction in blood level, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Placebo v Radium-223 dichloride (Xofigo, BAY88-8223) |

| | |
|---|---|
| Number of subjects included in analysis | 703 |
| Analysis specification | Pre-specified |
| Analysis type | other[53] |
| P-value | < 0.001 [54] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[53] - Comparison with placebo

[54] - >=30% reduction in blood level. Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

The null hypothesis for the comparison of >=50% reduction in blood level, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 703 |
| Analysis specification | Pre-specified |
| Analysis type | other[55] |
| P-value | = 0.106 [56] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[55] - Comparison with placebo

[56] - >=50% reduction in blood level.
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

The null hypothesis for the comparison of Confirmed PSA Response(>=50%), was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 703 |
| Analysis specification | Pre-specified |
| Analysis type | other[57] |
| P-value | = 0.032 [58] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[57] - Comparison with placebo

[58] - Confirmed PSA Response(>=50%).
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

## Secondary: Percentage of Subjects With PSA Response at EOT (Week 24 or at the Time the Subject Dies or Discontinues Treatment Phase)

| | |
|---|---|
| End point title | Percentage of Subjects With PSA Response at EOT (Week 24 or at the Time the Subject Dies or Discontinues Treatment Phase) |

End point description:

PSA levels were measured in subjects' blood at EOT (Week 24) and compared to baseline values. A confirmed PSA response (>/=50% reduction from baseline) was confirmed by a second PSA value approximately 4 weeks later.

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

End point timeframe:

At Baseline and End of Treatment (Week 24 or at the time the subject dies or discontinues treatment phase)

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 590[59] | 286[60] | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| >=30% reduction in blood level | 14.2 | 4.5 | | |
| >=50% reduction in blood level | 9 | 3.1 | | |
| Confirmed PSA Response (>=50%) | 6.1 | 1.7 | | |

Notes:

[59] - Subjects in the ITT population and had no missing values for this endpoint

[60] - Subjects in the ITT population and had no missing values for this endpoint

## Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of >=30% reduction in blood level, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 876 |
| Analysis specification | Pre-specified |
| Analysis type | other[61] |
| P-value | < 0.001 [62] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[61] - Comparison with placebo

[62] - >=30% reduction in blood level.
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

The null hypothesis for the comparison of >=50% reduction in blood level, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 876 |
| Analysis specification | Pre-specified |
| Analysis type | other[63] |
| P-value | = 0.002 [64] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[63] - Comparison with placebo

[64] - >=50% reduction in blood level.
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

| Statistical analysis title | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

The null hypothesis for the comparison of Confirmed PSA Response(>=50%), was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 876 |
| Analysis specification | Pre-specified |
| Analysis type | other[65] |
| P-value | = 0.005 [66] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[65] - Comparison with placebo

[66] - Confirmed PSA Response(>=50%).
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

## Secondary: Percentage Change From Baseline in PSA at Week 12

| | |
|---|---|
| End point title | Percentage Change From Baseline in PSA at Week 12 |

End point description:

PSA level was measured in subject's blood at Week 12 and the percent change from the baseline value was calculated (PSA level at week 12 minus PSA level at baseline)/(PSA level at baseline)*100.

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

End point timeframe:

At Baseline and Week 12

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 493[67] | 210[68] | | |
| Units: Percent change | | | | |
| least squares mean (standard error) | 83.3 (± 152.48) | 543.8 (± 233.69) | | |

Notes:

[67] - Subjects in the ITT population and had no missing values for this endpoint

[68] - Subjects in the ITT population and had no missing values for this endpoint

## Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Percentage change from baseline in PSA at Week 12, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 703 |
| Analysis specification | Pre-specified |
| Analysis type | other[69] |
| P-value | = 0.16 [70] |
| Method | ANCOVA |

Notes:

[69] - Comparison with placebo

[70] - Percentage change from baseline in PSA at Week 12.
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

## Secondary: Maximum Percentage Decrease From Baseline in PSA up to Week 12

| End point title | Maximum Percentage Decrease From Baseline in PSA up to Week 12 |
|---|---|

End point description:

PSA level was measured in subject's blood up to Week 12 and the maximum percent decrease from the baseline up to week 12 value was calculated as the minimum value of [(PSA level up to week 12 minus PSA level at baseline)/(PSA level at baseline)*100] by subject, and set to zero if no decrease from baseline.

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

End point timeframe:

From baseline up to Week 12

| **End point values** | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 581[71] | 283[72] | | |
| Units: Percentage change | | | | |
| least squares mean (standard error) | -13 (± 0.9) | -7.8 (± 1.28) | | |

Notes:

[71] - Subjects in the ITT population and had no missing values for this endpoint

[72] - Subjects in the ITT population and had no missing values for this endpoint

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Maximum Percentage Decrease from Baseline up to Week 12, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
|---|---|
| Number of subjects included in analysis | 864 |
| Analysis specification | Pre-specified |
| Analysis type | other[73] |
| P-value | = 0.004 [74] |
| Method | ANCOVA |

Notes:

[73] - Comparison with placebo

[74] - Maximum Percentage Decrease from Baseline up to Week 12.
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

## Secondary: Percentage Change From Baseline in PSA at EOT (Week 24 or at the Time the Subject Dies or Discontinues Treatment Phase)

| End point title | Percentage Change From Baseline in PSA at EOT (Week 24 or at the Time the Subject Dies or Discontinues Treatment Phase) |
|---|---|

End point description:

PSA level was measured in subject's blood at EOT (Week 24) and the percent change from the baseline value was calculated (PSA level at EOT minus PSA level at baseline)/(PSA level at baseline)*100.

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

End point timeframe:

At Baseline and End of Treatment (Week 24 or at the time the subject dies or discontinues treatment phase)

| **End point values** | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 590[75] | 286[76] | | |
| Units: Percentage change | | | | |
| least squares mean (standard error) | 144.3 (± 15.38) | 191.1 (± 22.1) | | |

Notes:

[75] - Subjects in the ITT population and had no missing values for this endpoint

[76] - Subjects in the ITT population and had no missing values for this endpoint

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Percentage change from baseline in PSA at EOT, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
|---|---|
| Number of subjects included in analysis | 876 |
| Analysis specification | Pre-specified |
| Analysis type | other[77] |
| P-value | = 0.009 [78] |
| Method | ANCOVA |

Notes:

[77] - Comparison with placebo

[78] - Percentage change from baseline in PSA at EOT.
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

## Secondary: Maximum Percentage Decrease From Baseline in PSA Response During the 24 Week Treatment Period

| End point title | Maximum Percentage Decrease From Baseline in PSA Response During the 24 Week Treatment Period |
|---|---|

End point description:

PSA level was measured in subject's blood during the 24 week treatment (up to EOT) and the maximum percent decrease from baseline during the 24 Week treatment value was calculated as the minimum value of [(PSA level up to week 24 minus PSA level at baseline)/(PSA level at baseline)*100] by subject, and set to zero if no decrease from baseline.

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

End point timeframe:

From baseline to End of Treatment (Week 24; 4 weeks post last injection)

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 590[79] | 286[80] | | |
| Units: Percentage change | | | | |
| least squares mean (standard error) | -16.4 (± 1.01) | -9.3 (± 1.45) | | |

Notes:

[79] - Subjects in the ITT population and had no missing values for this endpoint

[80] - Subjects in the ITT population and had no missing values for this endpoint

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Maximum Percentage Decrease from Baseline in PSA response During the 24 Week Treatment Period, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 876 |
| Analysis specification | Pre-specified |
| Analysis type | other[81] |
| P-value | < 0.001 [82] |
| Method | ANCOVA |

Notes:

[81] - Comparison with placebo

[82] - Maximum Percentage Decrease from Baseline in PSA response During the 24 Week Treatment Period.
Adjusting for the binary stratification factors, total ALP, current use of Bisphosphonates and prior use of Docetaxel.

### Secondary: Time to First Skeletal Related Event (SRE)

| End point title | Time to First Skeletal Related Event (SRE) |
|---|---|

End point description:

A skeletal related event was the use of external beam radiotherapy to relieve skeletal symptoms or the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral) or the occurrence of spinal cord compression or a tumour related orthopaedic surgical intervention. For all other events, the start date of the event/medication/therapy was used as the time of the event. If an event had not occurred at the time of the analysis or the subject had been lost to follow-up, the time-to-event variables will be censored at the last disease assessment date.

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

End point timeframe:

From randomization to first SRE until the data cut-off date (10 Oct 2014) approximately 3 years after start of enrollment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[83] | 307[84] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 16.4 (14.3 to 18.3) | 8.1 (6.7 to 11.9) | | |

Notes:

[83] - The ITT population was all randomized subjects

[84] - The ITT population was all randomized subjects

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of time to first SRE, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists. The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
|---|---|
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[85] |
| P-value | = 0.00012 [86] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.657 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.529 |
| upper limit | 0.814 |

Notes:

[85] - Comparison with placebo

[86] - Time to first Skeletal Related Event (SRE).
Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

### Secondary: Time to Occurrence of First Use of External Beam Radiation Therapy (EBRT) to Relieve Skeletal Symptoms

| End point title | Time to Occurrence of First Use of External Beam Radiation Therapy (EBRT) to Relieve Skeletal Symptoms |
|---|---|

End point description:

The start date of therapy was used as the time of the event. If an event had not occurred at the time of the analysis or the subject had been lost to follow-up, the time-to-event variables will be censored at the last disease assessment date.

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

End point timeframe:

From randomization to first EBRT until the data cut-off date (10 Oct 2014) approximately 3 years after start of enrollment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[87] | 307[88] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 18 (15.9 to 20.6) | 10.7 (7.6 to 18.5) | | |

Notes:

[87] - The ITT population was all randomized subjects

[88] - The ITT population was all randomized subjects

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of time to EBRT, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists. The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[89] |
| P-value | = 0.00008 [90] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.639 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.511 |
| upper limit | 0.8 |

Notes:

[89] - Comparison with placebo

[90] - Time to External Beam Radiotherapy.
Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

### Secondary: Time to Occurrence of First Use of Radioisotopes to Relieve Skeletal Symptoms

| End point title | Time to Occurrence of First Use of Radioisotopes to Relieve Skeletal Symptoms |
|---|---|

End point description:

The start date of the radioisotopes was used as the time of the event. If an event had not occurred at the time of the analysis or the subject had been lost to follow-up, the time-to-event variables will be censored at the last disease assessment date. '99999' indicates that values were not reported since median survival time was not reached.

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

End point timeframe:

From randomization to first use of radioisotopes until the data cut-off date (10 Oct 2014)approximately 3 years after start of enrollment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[91] | 307[92] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Notes:

[91] - The ITT population was all randomized subjects.

[92] - The ITT population was all randomized subjects.

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Time to Receiving Radio-isotope, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists. The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[93] |
| P-value | = 0.00191 [94] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.344 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.17 |
| upper limit | 0.695 |

Notes:

[93] - Comparison with placebo

[94] - Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

### Secondary: Time to Occurrence of First New Symptomatic Pathological Bone Fractures, Vertebral and Non-vertebral

| End point title | Time to Occurrence of First New Symptomatic Pathological Bone Fractures, Vertebral and Non-vertebral |
|---|---|

End point description:

The start date of the event was used as the time of the event. If an event had not occurred at the time of the analysis or the subject had been lost to follow-up, the time-to-event variables will be censored at the last disease assessment date. '99999' indicates that values were not reported since median survival time was not reached.

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

End point timeframe:

From randomization to occurrence of first new symptomatic pathological bone fractures until the data cut-off date (10 Oct 2014) approximately 3 years after start of enrollment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[95] | 307[96] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Notes:

[95] - The ITT population was all randomized subjects

[96] - The ITT population was all randomized subjects

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Time to Pathological Bone Fracture, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists. The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
|---|---|
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[97] |
| P-value | = 0.53277 [98] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.847 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.504 |
| upper limit | 1.426 |

Notes:

[97] - Comparison with placebo.

[98] - Time to Pathological Bone Fracture.
Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

### Secondary: Time to Occurrence of First Tumor Related Orthopedic Surgical Intervention

| End point title | Time to Occurrence of First Tumor Related Orthopedic Surgical Intervention |
|---|---|

End point description:

The start date of the intervention was used as the time of the event. If an event had not occurred at the time of the analysis or the subject had been lost to follow-up, the time-to-event variables will be censored at the last disease assessment date. '99999' indicates that values were not reported since median survival time was not reached.

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

End point timeframe:

From randomization to occurrence of first tumor related orthopedic surgical intervention until the data cut-off date (10 Oct 2014) approximately 3 years after start of enrollment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[99] | 307[100] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Notes:

[99] - The ITT population was all randomized subjects

[100] - The ITT population was all randomized subjects

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Time to Surgical Intervention, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists. The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[101] |
| P-value | = 0.89567 [102] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.949 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.435 |
| upper limit | 2.07 |

Notes:

[101] - Comparison with placebo

[102] - Time to Surgical Intervention.
Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

### Secondary: Time to Occurrence of First Spinal Cord Compression

| End point title | Time to Occurrence of First Spinal Cord Compression |
|---|---|

End point description:

The start date of the compression was used as the time of the event. If an event had not occurred at the time of the analysis or the subject had been lost to follow-up, the time-to-event variables will be censored at the last disease assessment date. '99999' indicates that values were not reported since median survival time was not reached.

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

End point timeframe:

From randomization to first spinal cord compression until the data cut-off date (10 Oct 2014) approximately 3 years after start of enrollment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[103] | 307[104] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Notes:

[103] - The ITT population was all randomized subjects

[104] - The ITT population was all randomized subjects

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Time to Spinal Cord Compression, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists. The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[105] |
| P-value | = 0.14486 [106] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.404 |
| upper limit | 1.145 |

Notes:

[105] - Comparison with placebo

[106] - Time to Spinal Cord Compression.
Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

### Secondary: Time to Occurrence of First Start of any Other Anti-cancer Treatment

| End point title | Time to Occurrence of First Start of any Other Anti-cancer Treatment |
|---|---|

End point description:

The start date of the treatment was used as the time of the event. If an event had not occurred at the time of the analysis or the subject had been lost to follow-up, the time-to-event variables will be censored at the last disease assessment date.

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

End point timeframe:

From randomization to first start of any other anti-cancer treatment until the data cut-off date (10 Oct 2014) approximately 3 years after start of enrollment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[107] | 307[108] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 15.4 (12.6 to 17) | 12.7 (11 to 14.7) | | |

Notes:

[107] - The ITT population was all randomized subjects

[108] - The ITT population was all randomized subjects

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Time to Other Cancer Treatment, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists. The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[109] |
| P-value | = 0.00932 [110] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.727 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.571 |
| upper limit | 0.925 |

Notes:

[109] - comparison with placebo

[110] - Time to Other Cancer Treatment.
Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

### Secondary: Time to Occurrence of First Deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG PS) by at Least 2 Points From Baseline

| End point title | Time to Occurrence of First Deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG PS) by at Least 2 Points From Baseline |
|---|---|

End point description:

ECOG scores were: 0 = fully active; 1 = restricted in physically strenuous activity; 2 = ambulatory and capable of all self-care but unable to work; 3 = capable of only limited self-care; 4 = completely disabled; 5 = death. The visit at which a 2-point or more deterioration in PS was observed was the time of the event. ECOG was assessed at every visit. If a marked deterioration in PS had not occurred at the time of the analysis or the subject was lost to follow-up, the time-to-event variables were censored at the last assessment date.

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

End point timeframe:

From randomization to first deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG PS) until the data cut-off date (10 Oct 2014) approximately 3 years after start of enrollment

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[111] | 307[112] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 23.4 (20.4 to 26.5) | 18.4 (13.1 to 24.5) | | |

Notes:

[111] - The ITT population was all randomized subjects

[112] - The ITT population was all randomized subjects

### Statistical analyses

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

Statistical analysis description:

The null hypothesis for the comparison of Time to Marked Deterioration of ECOG PS, was that there was no difference between Alpharadin and placebo for that endpoint; the alternative hypothesis was that a difference exists. The hazard ratio (Alpharadin:Placebo) was from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

| | |
|---|---|
| Comparison groups | Radium-223 dichloride (Xofigo, BAY88-8223) v Placebo |
| Number of subjects included in analysis | 921 |
| Analysis specification | Pre-specified |
| Analysis type | other[113] |
| P-value | = 0.00187 [114] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.546 |
| upper limit | 0.873 |

Notes:

[113] - Comparison with placebo

[114] - Time to Marked Deterioration of ECOG PS.
Stratified by total ALP, current use of bisphosphonates and prior use of Docetaxel.

### Other pre-specified: Number of Subjects With Eastern Cooperative Oncology Group Performance Status (ECOG PS) at Week 0

| End point title | Number of Subjects With Eastern Cooperative Oncology Group Performance Status (ECOG PS) at Week 0 |
|---|---|

End point description:

ECOG PS was defined as: 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 (eg, light house work, office work); 2 = Ambulatory and capable of all self-care but unable to carry out work activities. Up and about >50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair; or 5 = Dead.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Week 0

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 600[115] | 305[116] | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| ECOG Grade 0 | 136 | 72 | | |
| ECOG Grade 1 | 376 | 191 | | |
| ECOG Grade 2 | 82 | 40 | | |
| ECOG Grade 3 | 6 | 1 | | |
| ECOG Grade 4 | 0 | 0 | | |
| ECOG Grade 5 | 0 | 0 | | |
| Missing | 0 | 1 | | |

Notes:

[115] - Subjects in the ITT population and with ECOG analyzed

[116] - Subjects in the ITT population and with ECOG analyzed

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of Subjects With Eastern Cooperative Oncology Group Performance Status (ECOG PS) at Week 8

| End point title | Number of Subjects With Eastern Cooperative Oncology Group Performance Status (ECOG PS) at Week 8 |
|---|---|

End point description:

ECOG PS was defined as: 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 (eg, light house work, office work); 2 = Ambulatory and capable of all self-care but unable to carry out work activities. Up and about >50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair >50% of waking hours; 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair; or 5 = Dead.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Week 8

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 569[117] | 267[118] | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| ECOG Grade 0 | 133 | 49 | | |
| ECOG Grade 1 | 315 | 142 | | |
| ECOG Grade 2 | 103 | 53 | | |

| | | | | |
|---|---|---|---|---|
| ECOG Grade 3 | 13 | 15 | | |
| ECOG Grade 4 | 0 | 3 | | |
| ECOG Grade 5 | 1 | 1 | | |
| Missing | 4 | 4 | | |

Notes:

[117] - Subjects in the ITT population and with ECOG analyzed

[118] - Subjects in the ITT population and with ECOG analyzed

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects With Eastern Cooperative Oncology Group Performance Status (ECOG PS) at Week 16

| End point title | Number of Subjects With Eastern Cooperative Oncology Group Performance Status (ECOG PS) at Week 16 |
|---|---|

End point description:

ECOG PS was defined as: 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 (eg, light house work, office work); 2 = Ambulatory and capable of all self-care but unable to carry out work activities. Up and about >50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair >50% of waking hours; 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair; or 5 = Dead.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Week 16

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 471[119] | 196[120] | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| ECOG Grade 0 | 101 | 29 | | |
| ECOG Grade 1 | 257 | 113 | | |
| ECOG Grade 2 | 85 | 42 | | |
| ECOG Grade 3 | 19 | 11 | | |
| ECOG Grade 4 | 4 | 0 | | |
| ECOG Grade 5 | 0 | 0 | | |
| Missing | 5 | 1 | | |

Notes:

[119] - Subjects in the ITT population and with ECOG analyzed

[120] - Subjects in the ITT population and with ECOG analyzed

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects With Eastern Cooperative Oncology Group Performance Status (ECOG PS) at Week 24

| End point title | Number of Subjects With Eastern Cooperative Oncology Group Performance Status (ECOG PS) at Week 24 |
|---|---|

End point description:

ECOG PS was defined as: 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 (eg, light house work, office work); 2 = Ambulatory and capable of all self-care but unable to carry out work activities. Up and about >50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair >50% of waking hours; 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair; or 5 = Dead.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Week 24

| **End point values** | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363[121] | 138[122] | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| ECOG Grade 0 | 74 | 22 | | |
| ECOG Grade 1 | 181 | 66 | | |
| ECOG Grade 2 | 85 | 36 | | |
| ECOG Grade 3 | 17 | 10 | | |
| ECOG Grade 4 | 5 | 4 | | |
| ECOG Grade 5 | 0 | 0 | | |
| Missing | 1 | 0 | | |

Notes:

[121] - Subjects in the ITT population and with ECOG analyzed

[122] - Subjects`in the ITT population and with ECOG analyzed

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Absolute Scores for Functional Assessment of Cancer Therapy – Prostate (FACT-P) Trial Outcome Index (TOI)

| End point title | Absolute Scores for Functional Assessment of Cancer Therapy – Prostate (FACT-P) Trial Outcome Index (TOI) |
|---|---|

End point description:

The FACT-P was 27 questions relating to 4 domains: physical, social/family, emotional, and functional well-being. It was supplemented by 12 questions relating to prostate cancer. The absolute score for the FACT-P TOI domain (physical and social well-being and prostate specific score) was calculated for each visit. Prostate Cancer Trial Outcome Index (TOI): Physical Well-being (PWB) + Functional Well-being (FWB) + Prostate Cancer (PCS). Score ranges from 0 (worst) to 104 (best).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline, Week 16, Week 24, and Follow-up Visit 2 (Week 42)

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[123] | 307[124] | | |
| Units: Scores on a scale | | | | |
| median (full range (min-max)) | | | | |
| Week 0 (Baseline) | 65 (17 to 104) | 64 (23 to 96) | | |
| Week 16 | 65 (11 to 98) | 61.31 (19 to 96.5) | | |
| Week 24 | 61 (17 to 102) | 60 (17 to 97) | | |
| Follow-up Visit 2 (Week 42) | 61 (10 to 95) | 60.5 (16.7 to 97) | | |

Notes:

[123] - The ITT population was all randomized subjects

[124] - The ITT population was all randomized subjects

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Changes From Baseline for FACT-P Trial Outcome Index (TOI) at Week 16, Week 24, and Follow-up Visit 2 (Week 42)

| End point title | Changes From Baseline for FACT-P Trial Outcome Index (TOI) at Week 16, Week 24, and Follow-up Visit 2 (Week 42) |
|---|---|

End point description:

The FACT-P was 27 questions relating to 4 domains: physical, social/family, emotional, and functional well-being. It was supplemented by 12 questions relating to prostate cancer. The absolute score for the FACT-P TOI domain (physical and social well-being and prostate specific score) was calculated for each visit. Possible scores were 0 to 104; the higher the score, the better the quality of life. The changes from baseline (range -104 to 104) in the domain FACT-P TOI were summarized using descriptive statistics at Week 16, Week 24, and Follow-up Visit 2.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline, Week 16, Week 24, and Follow-up Visit 2 (Week 42)

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[125] | 307[126] | | |
| Units: Scores on a scale | | | | |
| median (full range (min-max)) | | | | |
| At Week 16 | -1.55 (-49.3 to 38) | -4.15 (-43 to 46) | | |
| At Week 24 | -4 (-60.4 to 40) | -5.67 (-39 to 41) | | |
| At Follow-up Visit 2 (Week 42) | -5 (-89 to 44.5) | -5.5 (-47.4 to 25) | | |

Notes:

[125] - The ITT population was all randomized subjects

[126] - The ITT population was all randomized subjects

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Absolute Scores for Physical Well Being, Social/Family Well Being, Emotional Well Being, Functional Well Being, and the Prostate Cancer Subscale at Week 16

| End point title | Absolute Scores for Physical Well Being, Social/Family Well Being, Emotional Well Being, Functional Well Being, and the Prostate Cancer Subscale at Week 16 |
|---|---|

End point description:

The FACT-P was 27 questions relating to 4 domains: physical, social/family, emotional, and functional well-being and was supplemented by 12 questions relating to prostate cancer. Possible scores for each subscale were 0 to 28; 0 to 28; 0 to 24; 0 to 28; and 0 to 48, respectively. All FACT-P items are scored on a scale of 0-4 representing the extent to which the item reflects the experience of the individual completing the instrument (0 – Not at all; 4 – Very much). Higher scores indicate better quality of life. The absolute score of the FACT-P total score was calculated at Week 16.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

At Week 16

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[127] | 307[128] | | |
| Units: Scores on a scale | | | | |
| median (full range (min-max)) | | | | |
| physical well being | 20 (3 to 28) | 19.83 (1 to 28) | | |
| social/family well being | 22 (0 to 28) | 21.5 (0 to 28) | | |
| emotional well being | 18 (0 to 24) | 16.8 (2 to 24) | | |
| functional well being | 16 (0 to 28) | 15 (0 to 28) | | |
| the prostate cancer subscale | 29 (1 to 46.9) | 27.6 (9 to 42.5) | | |

Notes:

[127] - The ITT population was all randomized subjects

[128] - The ITT population was all randomized subjects

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Absolute Scores for Physical Well Being, Social/Family Well Being, Emotional Well Being, Functional Well Being, and the Prostate Cancer Subscale at Week 24

| End point title | Absolute Scores for Physical Well Being, Social/Family Well Being, Emotional Well Being, Functional Well Being, and the Prostate Cancer Subscale at Week 24 |
|---|---|

End point description:

The FACT-P was 27 questions relating to 4 domains: physical, social/family, emotional, and functional well-being and was supplemented by 12 questions relating to prostate cancer. Possible scores for each subscale were 0 to 28; 0 to 28; 0 to 24; 0 to 28; and 0 to 48, respectively. All FACT-P items are scored on a scale of 0-4 representing the extent to which the item reflects the experience of the individual completing the instrument (0 – Not at all; 4 – Very much). Higher scores indicate better quality of life. The absolute score of the FACT-P total score was calculated at Week 24.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

At Week 24

| **End point values** | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[129] | 307[130] | | |
| Units: Scores on a scale | | | | |
| median (full range (min-max)) | | | | |
| physical well being | 19 (3 to 28) | 18.67 (3 to 28) | | |
| social/family well being | 21 (0 to 28) | 21 (9 to 28) | | |
| emotional well being | 17 (4 to 24) | 16 (1.2 to 24) | | |
| functional well being | 15 (0 to 28) | 14 (0 to 28) | | |
| the prostate cancer subscale | 28 (3.6 to 46) | 27.64 (5 to 43) | | |

Notes:

[129] - The ITT population was all randomized subjects

[130] - The ITT population was all randomized subjects

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Absolute Scores for Physical Well Being, Social/Family Well Being, Emotional Well Being, Functional Well Being, and the Prostate Cancer Subscale at Follow-up Visit 2 (Week 42)

| End point title | Absolute Scores for Physical Well Being, Social/Family Well Being, Emotional Well Being, Functional Well Being, and the Prostate Cancer Subscale at Follow-up Visit 2 (Week 42) |
|---|---|

End point description:

The FACT-P was 27 questions relating to 4 domains: physical, social/family, emotional, and functional well-being and was supplemented by 12 questions relating to prostate cancer. Possible scores for each subscale were 0 to 28; 0 to 28; 0 to 24; 0 to 28; and 0 to 48, respectively. All FACT-P items are scored on a scale of 0-4 representing the extent to which the item reflects the experience of the individual completing the instrument (0 – Not at all; 4 – Very much). Higher scores indicate better quality of life. The absolute score of the FACT-P total score was calculated at Follow-up Visit 2.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

At Follow-up Visit 2 (Week 42)

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[131] | 307[132] | | |
| Units: Scores on a scale | | | | |
| median (full range (min-max)) | | | | |
| physical well being | 19 (0 to 28) | 18 (1 to 28) | | |
| social/family well being | 22 (0 to 28) | 22 (9 to 33.8) | | |
| emotional well being | 17 (0 to 24) | 16 (3 to 24) | | |
| functional well being | 14 (1 to 28) | 14 (4 to 28) | | |
| the prostate cancer subscale | 28 (3 to 42) | 29 (6.5 to 43) | | |

Notes:

[131] - The ITT population was all randomized subjects

[132] - The ITT population was all randomized subjects

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Absolute Scores for FACT-P Total Score at Week 16, Week 24, and Follow-up Visit 2 (Week 42)

| End point title | Absolute Scores for FACT-P Total Score at Week 16, Week 24, and Follow-up Visit 2 (Week 42) |
|---|---|

End point description:

The FACT-P was 27 questions relating to 4 domains: physical, social/family, emotional, and functional well-being. It was supplemented by 12 questions relating to prostate cancer. The absolute score of the FACT-P total score (physical, social/family, emotional, and functional well-being and prostate specific score) was calculated at Week 16, Week 24, and Follow-up Visit 2.FACT-P Total Score: Physical Well-being (PWB) + Social/Family Well-being (SWB) + Emotional Well-being (EWB) + Functional Well-being (FWB) + Prostate Cancer (PCS). Score ranges from 0 (worst) to 156 (best).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

At Week 16, Week 24, and Follow-up Visit 2 (Week 42)

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[133] | 307[134] | | |
| Units: Scores on a scale | | | | |
| median (full range (min-max)) | | | | |
| At Week 16 | 100.68 (30 to 147) | 99.9 (33.7 to 144) | | |
| At Week 24 | 98 (41.8 to 152) | 97.5 (47 to 149) | | |
| At Follow-up Visit 2 (Week 42) | 97.83 (41 to 145) | 97.38 (40.9 to 147.8) | | |

Notes:

[133] - The ITT population was all randomized subjects

[134] - The ITT population was all randomized subjects

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Change From Baseline for FACT-P Total Score at Week 16, Week 24, and Follow-up Visit 2 (Week 42)

| End point title | Change From Baseline for FACT-P Total Score at Week 16, Week 24, and Follow-up Visit 2 (Week 42) |
|---|---|

End point description:

The FACT-P was 27 questions relating to 4 domains: physical, social/family, emotional, and functional well-being. It was supplemented by 12 questions relating to prostate cancer. Total possible score was 156; a higher score indicates a better quality of life. The changes from baseline in the FACT-P total score (physical, social/family, emotional, and functional well-being and prostate specific score) were calculated at Week 16, Week 24, and Follow-up Visit 2. Possible range was -156 to 156.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline, Week 16, Week 24, and Follow-up Visit 2 (week 42)

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[135] | 307[136] | | |
| Units: Scores on a scale | | | | |
| median (full range (min-max)) | | | | |
| At Week 16 | -2 (-58 to 58) | -5.67 (-58 to 47) | | |
| At Week 24 | -5 (-67.2 to 63.5) | -9.4 (-42.8 to 48.8) | | |
| At Follow-up Visit 2 (Week 42) | -6.17 (-97 to 63.5) | -7 (-54.7 to 23.7) | | |

Notes:

[135] - The ITT population was all randomized subjects

[136] - The ITT population was all randomized subjects

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Absolute Scores for Functional Assessment of Cancer Therapy – General (FACT-G) Total Score at Week 16, Week 24, and Follow-up Visit 2 (Week 42)

| End point title | Absolute Scores for Functional Assessment of Cancer Therapy – General (FACT-G) Total Score at Week 16, Week 24, and Follow-up Visit 2 (Week 42) |
|---|---|

End point description:

The FACT-G instrument consisted of 27 questions relating to 4 domains: physical, social/family, emotional, and functional well-being. The FACT-G absolute total score (physical, social/family, emotional, and functional well-being) was calculated at Week 16, Week 24, and Follow-up Visit 2. FACT-G Total Score: Physical Well-being (PWB) + Social/Family Well-being (SWB) + Emotional Well-being (EWB) + Functional Well-being (FWB). Score ranges from 0 (worst) to 108 (best).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

At Week 16, Week 24, and Follow-up Visit 2 (Week 42)

| **End point values** | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[137] | 307[138] | | |
| Units: Scores on a scale | | | | |
| median (full range (min-max)) | | | | |
| At Week 16 | 73 (17 to 106) | 72 (27.7 to 108) | | |
| At Week 24 | 71 (28 to 107) | 69 (37 to 106) | | |
| At Follow-up Visit 2 (Week 42) | 70 (22 to 107) | 70.25 (32.2 to 104.8) | | |

Notes:

[137] - The ITT population was all randomized subjects

[138] - The ITT population was all randomized subjects

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Change From Baseline for FACT-G Total Score at Week 16, Week 24, and Follow-up Visit 2 (Week 42)

| End point title | Change From Baseline for FACT-G Total Score at Week 16, Week 24, and Follow-up Visit 2 (Week 42) |
|---|---|

End point description:

The FACT-G instrument consisted of 27 questions relating to 4 domains: physical, social/family, emotional, and functional well-being. Total possible score was 108; a higher score indicates a better quality of life. The changes from baseline in the FACT-G total score (physical, social/family, emotional, and functional well-being) were calculated at Week 16, Week 24, and Follow-up Visit 2. Possible range was -108 to 108.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline, Week 16, Week 24, and Follow-up Visit 2 (Week 42)

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 614[139] | 307[140] | | |
| Units: Scores on a scale | | | | |
| median (full range (min-max)) | | | | |
| At Week 16 | -1 (-38.3 to 40) | -4 (-53 to 32.8) | | |
| At Week 24 | -4.08 (-49 to 49.5) | -7 (-35.8 to 41.8) | | |
| At Follow-up Visit 2 (Week 42) | -3.67 (-58 to 40.5) | -6 (-33.8 to 18.7) | | |

Notes:

[139] - The ITT population was all randomized subjects

[140] - The ITT population was all randomized subjects

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of Subjects in the Euro Quality of Life (EQ-5D) Components for Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression at Week 16

| End point title | Number of Subjects in the Euro Quality of Life (EQ-5D) Components for Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression at Week 16 |
|---|---|

End point description:

The EQ-5D questionnaire was given to the subject at each visit. The EQ-5D questionnaire consisted of 5 ordinal categorical responses (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Number of subjects with EQ-5D at Week 16, as measured by this questionnaire, was counted. The scores for the EQ-5D dimensions are assigned according to the level of problems reported (1 'no problems'; 2 'some problems'; 3 'extreme problems').

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Week 16

| End point values | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 477[141] | 205[142] | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| mobility - Grade 1 | 191 | 64 | | |
| mobility - Grade 2 | 278 | 129 | | |
| mobility - Grade 3 | 7 | 10 | | |
| mobility - Missing | 1 | 2 | | |
| self-care - Grade 1 | 346 | 140 | | |
| self-care - Grade 2 | 123 | 54 | | |
| self-care - Grade 3 | 7 | 10 | | |
| self-care - Missing | 1 | 1 | | |

| | | | | |
|---|---|---|---|---|
| usual activities - Grade 1 | 199 | 67 | | |
| usual activities - Grade 2 | 233 | 105 | | |
| usual activities - Grade 3 | 44 | 32 | | |
| usual activities - Missing | 1 | 1 | | |
| pain/discomfort - Grade 1 | 79 | 23 | | |
| pain/discomfort - Grade 2 | 351 | 159 | | |
| pain/discomfort - Grade 3 | 46 | 22 | | |
| pain/discomfort - Missing | 1 | 1 | | |
| anxiety/depression - Grade 1 | 285 | 104 | | |
| anxiety/depression - Grade 2 | 171 | 95 | | |
| anxiety/depression - Grade 3 | 15 | 4 | | |
| anxiety/depression - Missing | 6 | 2 | | |

Notes:

[141] - The ITT population was all randomized subjects with with EQ-5D analyzed.

[142] - The ITT population was all randomized subjects with with EQ5D analysed.

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects in the Euro Quality of Life (EQ-5D) Components for Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression at Week 24

| | |
|---|---|
| End point title | Number of Subjects in the Euro Quality of Life (EQ-5D) Components for Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression at Week 24 |

End point description:

The EQ-5D questionnaire was given to the subject at each visit. The EQ-5D questionnaire consisted of 5 ordinal categorical responses (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Number of subjects with EQ-5D at Week 24, as measured by this questionnaire, was counted. The scores for the EQ-5D dimensions are assigned according to the level of problems reported (1 'no problems'; 2 'some problems'; 3 'extreme problems').

| | |
|---|---|
| End point type | Other pre-specified |

End point timeframe:

Week 24

| **End point values** | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 368[143] | 140[144] | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| mobility - Grade 1 | 129 | 39 | | |
| mobility - Grade 2 | 225 | 93 | | |
| mobility - Grade 3 | 11 | 5 | | |
| mobility - Missing | 3 | 3 | | |
| self-care - Grade 1 | 256 | 89 | | |
| self-care - Grade 2 | 102 | 46 | | |
| self-care - Grade 3 | 6 | 3 | | |

| | | | | |
|---|---|---|---|---|
| self-care - Missing | 4 | 2 | | |
| usual activities - Grade 1 | 140 | 38 | | |
| usual activities - Grade 2 | 187 | 79 | | |
| usual activities - Grade 3 | 37 | 20 | | |
| usual activities - Missing | 4 | 3 | | |
| pain/discomfort - Grade 1 | 56 | 21 | | |
| pain/discomfort - Grade 2 | 270 | 95 | | |
| pain/discomfort - Grade 3 | 39 | 21 | | |
| pain/discomfort - Missing | 3 | 3 | | |
| anxiety/depression - Grade 1 | 195 | 64 | | |
| anxiety/depression - Grade 2 | 159 | 71 | | |
| anxiety/depression - Grade 3 | 10 | 2 | | |
| anxiety/depression - Missing | 4 | 3 | | |

Notes:

[143] - The ITT population was all randomized subjects with with EQ-5D analyzed.

[144] - The ITT population was all randomized subjects with with EQ5D analysed.

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects in the Euro Quality of Life (EQ-5D) Components for Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression at Follow-up Visit 8 (Week 139)

| | |
|---|---|
| End point title | Number of Subjects in the Euro Quality of Life (EQ-5D) Components for Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression at Follow-up Visit 8 (Week 139) |

End point description:

The EQ-5D questionnaire was given to the subject at each visit. The EQ-5D questionnaire consisted of 5 ordinal categorical responses (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Number of subjects with EQ-5D at follow-up visit 8, as measured by this questionnaire, was counted. The scores for the EQ-5D dimensions are assigned according to the level of problems reported (1 'no problems'; 2 'some problems'; 3 'extreme problems').

| | |
|---|---|
| End point type | Other pre-specified |

End point timeframe:

Follow-up Visit 8 (Week 139)

| **End point values** | Radium-223 dichloride (Xofigo, BAY88-8223) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41[145] | 13[146] | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| mobility - Grade 1 | 9 | 2 | | |
| mobility - Grade 2 | 30 | 10 | | |
| mobility - Grade 3 | 1 | 1 | | |
| mobility - Missing | 1 | 0 | | |
| self-care - Grade 1 | 26 | 7 | | |
| self-care - Grade 2 | 12 | 3 | | |

| | | | | |
|---|---|---|---|---|
| self-care - Grade 3 | 2 | 3 | | |
| self-care - Missing | 1 | 0 | | |
| usual activities - Grade 1 | 13 | 2 | | |
| usual activities - Grade 2 | 19 | 7 | | |
| usual activities - Grade 3 | 8 | 4 | | |
| usual activities - Missing | 1 | 0 | | |
| pain/discomfort - Grade 1 | 5 | 1 | | |
| pain/discomfort - Grade 2 | 32 | 11 | | |
| pain/discomfort - Grade 3 | 3 | 1 | | |
| pain/discomfort - Missing | 1 | 0 | | |
| anxiety/depression - Grade 1 | 24 | 6 | | |
| anxiety/depression - Grade 2 | 15 | 7 | | |
| anxiety/depression - Grade 3 | 1 | 0 | | |
| anxiety/depression - Missing | 1 | 0 | | |

Notes:

[145] - The ITT population was all randomized subjects with with EQ-5D analyzed.

[146] - The ITT population was all randomized subjects with with EQ-5D analyzed.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from first dose of study drug to the final data as of 10OCT2014

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 11.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Radium-223 Dichloride (Xofigo, BAY88-8223) |

Reporting group description:

Subjects received BSoC plus radium-223 50 kBq/kg body weight for 6 IV administrations separated by 4 weeks intervals.

| | |
|---|---|
| Reporting group title | Placebo Randomized, Then Switched to Radium-223 Dichloride |

Reporting group description:

Subjects received BSoC plus isotonic saline for 6 IV administrations separated by 4 weeks intervals from first dose of study drug to data cut-off date of 15 July 2011; Subjects received radium-223 50 kBq/kg body weight for 6 intravenous administrations separated by 4 weeks intervals from 15 July 2011 to the end of study.

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

Reporting group description:

Subjects received BSoC plus isotonic saline for 6 IV administrations separated by 4 weeks intervals.

| Serious adverse events | Radium-223 Dichloride (Xofigo, BAY88-8223) | Placebo Randomized, Then Switched to Radium-223 Dichloride | Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 286 / 600 (47.67%) | 17 / 24 (70.83%) | 185 / 301 (61.46%) |
| number of deaths (all causes) | 520 | 18 | 251 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Benign neoplasm of bladder | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Metastases to liver | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 600 (0.67%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Metastases to lymph nodes | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 65 / 600 (10.83%) | 2 / 24 (8.33%) | 38 / 301 (12.62%) |
| occurrences causally related to treatment / all | 0 / 67 | 0 / 2 | 0 / 42 |
| deaths causally related to treatment / all | 0 / 53 | 0 / 2 | 0 / 35 |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Bone marrow tumour cell infiltration | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lymphangiosis carcinomatosa | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Benign urinary tract neoplasm | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to central nervous system | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 600 (0.83%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 4 / 600 (0.67%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 4 / 600 (0.67%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 4 | 0 / 0 | 0 / 1 |

| | | | |
|---|---|---|---|
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 6 / 600 (1.00%) | 0 / 24 (0.00%) | 9 / 301 (2.99%) |
| occurrences causally related to treatment / all | 4 / 7 | 0 / 0 | 1 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 600 (1.00%) | 0 / 24 (0.00%) | 6 / 301 (1.99%) |
| occurrences causally related to treatment / all | 6 / 9 | 0 / 0 | 1 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 600 (0.67%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 15 / 600 (2.50%) | 1 / 24 (4.17%) | 8 / 301 (2.66%) |
| occurrences causally related to treatment / all | 3 / 15 | 0 / 1 | 1 / 8 |
| deaths causally related to treatment / all | 0 / 6 | 0 / 1 | 0 / 2 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Drug intolerance | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Prostatic haemorrhage | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Scrotal oedema | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 3 / 301 (1.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic respiratory failure | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Emphysema | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 600 (1.00%) | 0 / 24 (0.00%) | 5 / 301 (1.66%) |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 600 (0.67%) | 0 / 24 (0.00%) | 3 / 301 (1.00%) |
| occurrences causally related to treatment / all | 3 / 8 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 7 / 600 (1.17%) | 0 / 24 (0.00%) | 6 / 301 (1.99%) |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 0 | 0 / 6 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 3 |
| Pneumonia aspiration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 6 / 600 (1.00%) | 0 / 24 (0.00%) | 3 / 301 (1.00%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Aggression | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intentional self-injury | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatic specific antigen increased | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Concussion | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis radiation | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Extradural haematoma | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 1 / 24 (4.17%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Fall | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intentional overdose | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sternal fracture | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Therapeutic agent toxicity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stent occlusion | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Medical device complication | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin laceration | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pain | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post-traumatic pain | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 3 / 301 (1.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 4 / 301 (1.33%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 4 / 301 (1.33%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 600 (0.67%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 3 / 301 (1.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 2 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| Acute coronary syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 3 / 301 (1.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Aphasia | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dementia | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Convulsion | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysarthria | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Monoparesis | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial palsy | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraparesis | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 3 / 301 (1.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraplegia | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 1 / 24 (4.17%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 21 / 600 (3.50%) | 1 / 24 (4.17%) | 16 / 301 (5.32%) |
| occurrences causally related to treatment / all | 0 / 21 | 0 / 1 | 0 / 16 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radicular syndrome | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nerve root compression | | | |
| subjects affected / exposed | 4 / 600 (0.67%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paresis cranial nerve | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 50 / 600 (8.33%) | 1 / 24 (4.17%) | 25 / 301 (8.31%) |
| occurrences causally related to treatment / all | 49 / 70 | 1 / 1 | 15 / 35 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Aplastic anaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 5 / 600 (0.83%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 5 / 6 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 14 / 600 (2.33%) | 1 / 24 (4.17%) | 3 / 301 (1.00%) |
| occurrences causally related to treatment / all | 11 / 14 | 1 / 1 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 8 / 600 (1.33%) | 0 / 24 (0.00%) | 4 / 301 (1.33%) |
| occurrences causally related to treatment / all | 2 / 8 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 4 / 301 (1.33%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecal incontinence | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 9 / 600 (1.50%) | 0 / 24 (0.00%) | 5 / 301 (1.66%) |
| occurrences causally related to treatment / all | 3 / 10 | 0 / 0 | 3 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 1 / 24 (4.17%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 11 / 600 (1.83%) | 0 / 24 (0.00%) | 7 / 301 (2.33%) |
| occurrences causally related to treatment / all | 6 / 20 | 0 / 0 | 1 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erosive duodenitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute prerenal failure | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 11 / 600 (1.83%) | 0 / 24 (0.00%) | 7 / 301 (2.33%) |
| occurrences causally related to treatment / all | 1 / 13 | 0 / 0 | 1 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Calculus ureteric | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 8 / 600 (1.33%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 4 / 600 (0.67%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 7 / 600 (1.17%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| Urinary incontinence | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal pain | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal tubular necrosis | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary bladder haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage urinary tract | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 10 / 600 (1.67%) | 0 / 24 (0.00%) | 9 / 301 (2.99%) |
| occurrences causally related to treatment / all | 1 / 10 | 0 / 0 | 0 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Musculoskeletal and connective tissue disorders** | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 61 / 600 (10.17%) | 1 / 24 (4.17%) | 50 / 301 (16.61%) |
| occurrences causally related to treatment / all | 6 / 76 | 0 / 1 | 6 / 56 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myalgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 5 / 600 (0.83%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 14 / 600 (2.33%) | 1 / 24 (4.17%) | 11 / 301 (3.65%) |
| occurrences causally related to treatment / all | 1 / 14 | 1 / 1 | 0 / 11 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal column stenosis | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Catheter related infection | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 10 / 600 (1.67%) | 0 / 24 (0.00%) | 3 / 301 (1.00%) |
| occurrences causally related to treatment / all | 1 / 12 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Listeriosis | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lobar pneumonia | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 8 / 600 (1.33%) | 0 / 24 (0.00%) | 2 / 301 (0.66%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 17 / 600 (2.83%) | 1 / 24 (4.17%) | 7 / 301 (2.33%) |
| occurrences causally related to treatment / all | 1 / 18 | 0 / 1 | 1 / 8 |
| deaths causally related to treatment / all | 1 / 5 | 0 / 0 | 0 / 0 |
| Pneumonia primary atypical | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyonephrosis | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 7 / 600 (1.17%) | 0 / 24 (0.00%) | 4 / 301 (1.33%) |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 5 / 600 (0.83%) | 0 / 24 (0.00%) | 6 / 301 (1.99%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess jaw | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis infective | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 5 / 600 (0.83%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cachexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Dehydration | | | |
| subjects affected / exposed | 12 / 600 (2.00%) | 0 / 24 (0.00%) | 3 / 301 (1.00%) |
| occurrences causally related to treatment / all | 10 / 20 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 600 (0.50%) | 0 / 24 (0.00%) | 1 / 301 (0.33%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 600 (0.17%) | 0 / 24 (0.00%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 600 (0.00%) | 1 / 24 (4.17%) | 0 / 301 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Radium-223 Dichloride (Xofigo, BAY88-8223) | Placebo Randomized, Then Switched to Radium-223 Dichloride | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 524 / 600 (87.33%) | 23 / 24 (95.83%) | 254 / 301 (84.39%) |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 74 / 600 (12.33%) | 2 / 24 (8.33%) | 44 / 301 (14.62%) |
| occurrences (all) | 74 | 2 | 45 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 12 / 600 (2.00%) | 3 / 24 (12.50%) | 4 / 301 (1.33%) |
| occurrences (all) | 13 | 3 | 4 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 45 / 600 (7.50%) | 2 / 24 (8.33%) | 26 / 301 (8.64%) |
| occurrences (all) | 53 | 2 | 30 |
| Headache | | | |
| subjects affected / exposed | 25 / 600 (4.17%) | 2 / 24 (8.33%) | 9 / 301 (2.99%) |
| occurrences (all) | 29 | 2 | 9 |
| Paraesthesia | | | |
| subjects affected / exposed | 16 / 600 (2.67%) | 2 / 24 (8.33%) | 4 / 301 (1.33%) |
| occurrences (all) | 16 | 2 | 4 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 161 / 600 (26.83%) | 8 / 24 (33.33%) | 81 / 301 (26.91%) |
| occurrences (all) | 247 | 10 | 104 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 59 / 600 (9.83%) | 2 / 24 (8.33%) | 15 / 301 (4.98%) |
| occurrences (all) | 71 | 2 | 16 |
| Neutropenia | | | |
| subjects affected / exposed | 28 / 600 (4.67%) | 2 / 24 (8.33%) | 3 / 301 (1.00%) |
| occurrences (all) | 37 | 3 | 4 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 157 / 600 (26.17%) | 9 / 24 (37.50%) | 73 / 301 (24.25%) |
| occurrences (all) | 192 | 10 | 86 |
| Asthenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 35 / 600 (5.83%) | 2 / 24 (8.33%) | 17 / 301 (5.65%) |
| occurrences (all) | 43 | 2 | 19 |
| Oedema peripheral | | | |
| subjects affected / exposed | 76 / 600 (12.67%) | 2 / 24 (8.33%) | 29 / 301 (9.63%) |
| occurrences (all) | 82 | 2 | 34 |
| Pyrexia | | | |
| subjects affected / exposed | 38 / 600 (6.33%) | 0 / 24 (0.00%) | 15 / 301 (4.98%) |
| occurrences (all) | 58 | 0 | 24 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 105 / 600 (17.50%) | 2 / 24 (8.33%) | 60 / 301 (19.93%) |
| occurrences (all) | 111 | 2 | 68 |
| Abdominal pain | | | |
| subjects affected / exposed | 21 / 600 (3.50%) | 2 / 24 (8.33%) | 13 / 301 (4.32%) |
| occurrences (all) | 21 | 2 | 15 |
| Diarrhoea | | | |
| subjects affected / exposed | 153 / 600 (25.50%) | 7 / 24 (29.17%) | 43 / 301 (14.29%) |
| occurrences (all) | 242 | 12 | 60 |
| Nausea | | | |
| subjects affected / exposed | 210 / 600 (35.00%) | 11 / 24 (45.83%) | 98 / 301 (32.56%) |
| occurrences (all) | 294 | 12 | 126 |
| Vomiting | | | |
| subjects affected / exposed | 108 / 600 (18.00%) | 3 / 24 (12.50%) | 34 / 301 (11.30%) |
| occurrences (all) | 151 | 3 | 45 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 47 / 600 (7.83%) | 0 / 24 (0.00%) | 21 / 301 (6.98%) |
| occurrences (all) | 54 | 0 | 22 |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 14 / 600 (2.33%) | 2 / 24 (8.33%) | 5 / 301 (1.66%) |
| occurrences (all) | 15 | 2 | 6 |
| Urinary retention | | | |
| subjects affected / exposed | 20 / 600 (3.33%) | 3 / 24 (12.50%) | 12 / 301 (3.99%) |
| occurrences (all) | 20 | 3 | 13 |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Insomnia | | | |
| subjects affected / exposed | 31 / 600 (5.17%) | 0 / 24 (0.00%) | 17 / 301 (5.65%) |
| occurrences (all) | 33 | 0 | 17 |
| Musculoskeletal and connective tissue disorders | | | |
| Joint swelling | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 2 / 24 (8.33%) | 3 / 301 (1.00%) |
| occurrences (all) | 2 | 2 | 3 |
| Bone pain | | | |
| subjects affected / exposed | 287 / 600 (47.83%) | 11 / 24 (45.83%) | 174 / 301 (57.81%) |
| occurrences (all) | 476 | 19 | 321 |
| Muscular weakness | | | |
| subjects affected / exposed | 8 / 600 (1.33%) | 2 / 24 (8.33%) | 15 / 301 (4.98%) |
| occurrences (all) | 8 | 2 | 18 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 13 / 600 (2.17%) | 4 / 24 (16.67%) | 8 / 301 (2.66%) |
| occurrences (all) | 13 | 4 | 11 |
| Urinary tract infection | | | |
| subjects affected / exposed | 47 / 600 (7.83%) | 5 / 24 (20.83%) | 22 / 301 (7.31%) |
| occurrences (all) | 55 | 8 | 23 |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 104 / 600 (17.33%) | 4 / 24 (16.67%) | 53 / 301 (17.61%) |
| occurrences (all) | 115 | 5 | 57 |
| Hypokalaemia | | | |
| subjects affected / exposed | 14 / 600 (2.33%) | 2 / 24 (8.33%) | 6 / 301 (1.99%) |
| occurrences (all) | 16 | 2 | 7 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 600 (0.33%) | 3 / 24 (12.50%) | 2 / 301 (0.66%) |
| occurrences (all) | 2 | 3 | 2 |
| Decreased appetite | | | |
| subjects affected / exposed | 36 / 600 (6.00%) | 1 / 24 (4.17%) | 13 / 301 (4.32%) |
| occurrences (all) | 39 | 1 | 13 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 May 2008 | The main rationale for this amendment was to make sure that the most important baseline parameters which might have an impact on the primary and secondary efficacy endpoints were well balanced between the two study groups.<br>Changes were:<br>1. Removed stratification factors for ECOG and any prior cytotoxic therapy<br>2. Added stratification factors for current use of bisphosphonates (yes or no) and prior use of docetaxel (yes or no). |
| 09 July 2008 | The main rationale for this amendment was to ensure that the study meets its stated objectives and yields robust conclusions, with adequate monitoring of data to detect emerging risk/benefit trends.<br>The key changes were:<br>1. Changed the sample size requirements for the study, from 450 subjects to 750 subjects randomized to account for the introduction of prior docetaxel use (yes/no) as a stratification factor during randomization<br>2. Planned for an unblinded IA of overall survival, to be reviewed by the IDMC<br>3. Changed PSA outcome and reporting to adhere to the Prostate Cancer Clinical Trials Working Group 2, published March, 2008. |
| 10 July 2009 | The main rationale for this amendment was to add clarifications to various sections in the protocol.<br>The key changes were:<br>1. Recommended that the screening hematology values were measured at a maximum of 1 week prior to randomization, and that the first injection was to be done as soon as possible after randomization<br>2. Clarified that while screening hemoglobin (Hb) was required to be 10 gram per deciliter (g/dL), the Hb level should not have been lower than 8 g/dL within 24 hours before any injection. If, prior to first injection, the subject had a Hb level of <8 g/dL, the subject should not have received study drug and would directly go into the follow-up phase<br>3. Clarified that it was accepted that after documented PSA progression, the PSA could decline pre-randomization, provided that the screening value was at least 5 ng/mL<br>4. Clarified that for traumatic fractures in weight-bearing bones during treatment phase, the study drug administration was to be delayed 2-4 weeks from the occurrence of the fracture<br>5. Changed the collection of date of death: To collect date of death for all subjects until the last subject had been followed for 3 years<br>6. Changedthe interval between injection of bisphosphonates and injection of study drug: Injection of bisphosphonates was to be done at least 2 hours before or after study drug administration<br>7. Changed the analysis of the primary efficacy endpoint from Cox proportional hazards regression to a stratified log-rank test<br>8. Changed the timing of sample size re-estimation, from approximately 350 subjects to 500-600 subjects enrolled<br>9. Changed the definition of the Safety population from all randomized subjects to all randomized subjects who had received at least 1 study drug treatment<br>10. Added sub-group analyses for safety and secondary efficacy variables in order to examine relationships between exposure and response. |

| | |
|---|---|
| 23 June 2010 | The main rationale for this amendment was to increase the sample size of the study due to an increase in the statistical power from 80% to 90%.<br>The rationale for the increase in power was to<br>1. Reduce the risk of false negative results<br>2. Get a better estimate of the primary efficacy endpoint<br>3. Get a better estimate of the secondary endpoints and subgroup analyses<br>4. Increase the body of safety data.<br>The same assumptions as in the original sample size calculation have been used for the calculation.<br>Changes:<br>1. Increased statistical power from 80% to 90% and increased the sample size from 750 to 900 with an increase in the accrual period from 24 to 30 months<br>2. Changed time of IA to be after approximately 320 events were observed<br>3. Made various minor clarifications and administrative changes. |
| 20 January 2011 | The main rationale for this amendment was to control for overall false positive rate (type I error rate) for the analysis of the secondary endpoints by using a gatekeeping procedure. Five secondary endpoints have been identified as main secondary endpoints and have been ordered hierarchically according to their clinical importance.<br>Changes were:<br>1. Defined 5 main secondary endpoints: including creating a composite endpoint for the time to occurrence of first SRE based on disease events already being collected and adding total ALP normalization,<br>2. Provided IDMC members with the opportunity to request analysis results for the main secondary endpoints provided that the IA met the efficacy criterion for overall survival; additionally, if the study was stopped based on the recommendation of the IDMC, then all remaining planned analyses were to be performed according to what was described in the final analysis in the protocol and the statistical analysis plan. |
| 24 June 2011 | The main rationale for this amendment was to offer placebo subjects who are still participating in the study (that is, have not withdrawn from the study) and who fulfil the eligibility criteria as defined in this protocol addendum, a full course of Alpharadin treatment (50 kBq/kg body weight administered 6 times, at intervals of 4 weeks).<br>1. Changes to study design and reference therapy (placebo) due to IDMC approval to unblind the study, allowing access to Alpharadin for subjects who previously received placebo<br>2. Added clarification regarding analysis populations to account for placebo subjects receiving Alpharadin after unblinding<br>3. Clarified definition of disease events. |

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.

'99999' in the reported data indicates that the data were not calculated. Decimal places were automatically truncated if last decimal equals zero.

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/23863050

http://www.ncbi.nlm.nih.gov/pubmed/25439694