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 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 Units: Subjects			
Age continuous Units: Years			
arithmetic mean	70.2	70.8	
standard deviation	± 8.1	± 7.87	-
Gender categorical 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 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. Changes were: 1. Removed stratification factors for ECOG and any prior cytotoxic therapy 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. The key changes were: 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 2. Planned for an unblinded IA of overall survival, to be reviewed by the IDMC 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. The key changes were: 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 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 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 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 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 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 7. Changed the analysis of the primary efficacy endpoint from Cox proportional hazards regression to a stratified log-rank test 8. Changed the timing of sample size re-estimation, from approximately 350 subjects to 500-600 subjects enrolled 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 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%. The rationale for the increase in power was to 1. Reduce the risk of false negative results 2. Get a better estimate of the primary efficacy endpoint 3. Get a better estimate of the secondary endpoints and subgroup analyses 4. Increase the body of safety data. The same assumptions as in the original sample size calculation have been used for the calculation. Changes: 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 2. Changed time of IA to be after approximately 320 events were observed 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. Changes were: 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, 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). 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 2. Added clarification regarding analysis populations to account for placebo subjects receiving Alpharadin after unblinding 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