Clinical trial results:
A three arm randomized, open-label Phase II study of radium-223 dichloride 50 kBq/kg (55 kBq/kg after implementation of NIST update) versus 80 kBq/kg (88 kBq/kg after implementation of NIST update), and versus 50 kBq/kg (55 kBq/kg after implementation of NIST update) in an extended dosing schedule in subjects with castration-resistant prostate cancer metastatic to the bone

Summary

EudraCT number	2013-003118-42
Trial protocol	DE IT CZ SE FI ES GB
Global end of trial date	09 August 2018

Results information

Result version number	v1 (current)
This version publication date	17 July 2019
First version publication date	17 July 2019

Trial information

Trial identification

Sponsor protocol code	BAY88-8223/16507

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02023697
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Co-primary objectives:

- To evaluate efficacy as measured by symptomatic skeletal event-free survival (SSE-FS) of radium-223 dichloride 55 kBq/kg for up to 6 doses compared to radium-223 dichloride 88 kBq/kg for up to 6 doses in subjects with CRPC metastatic to the bone; and

- To evaluate efficacy as measured by SSE-FS of radium223 dichloride 55 kBq/kg for up to 6 additional doses compared to no further radium-223 dichloride treatment in subjects with CRPC metastatic to the bone who previously received radium-223 dichloride 55 kBq/kg for up to 6 doses.

Protection of trial subjects:

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

Background therapy:

Concomitant best standard of care (BSoC) was permitted according to local clinical practice. Allowed treatments for prostate cancer included anti-androgenic therapies (detailed list in full protocol), surgery, and radiation. Subjects should have remained castrated during the study period (surgically or chemically). Initiation, maintenance or discontinuation of osteoclast inhibitors were left to the discretion of the investigator.

Cytotoxic chemotherapy for prostate cancer, other systemic radioisotopes, concomitant hemibody External beam radiotherapy (EBRT), or other investigational drugs were not to be used during the treatment period. If prohibited therapies were considered BSoC during the treatment period, further radium-223 dichloride administrations must have been discontinued, and if possible, prohibited treatment was not to be given within 30 days after the last injection of radium- 223 dichloride.

Evidence for comparator: -

Actual start date of recruitment	10 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Sweden: 14

Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Canada: 51
Country: Number of subjects enrolled	Israel: 70
Country: Number of subjects enrolled	China: 6
Country: Number of subjects enrolled	United States: 83
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	Australia: 56
Country: Number of subjects enrolled	Korea, Republic of: 39
Country: Number of subjects enrolled	France: 6
Worldwide total number of subjects	391
EEA total number of subjects	82

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)	89
From 65 to 84 years	292
85 years and over	10

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 391 participants assigned to treatment in the intention to treatment (ITT) analysis set, 370 participants (94.6%) received at least one dose of radium-223 dichloride, and a total of 21 participants (5.4%) never received treatment.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)

Arm description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses (“standard dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

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 dichloride (Xofigo, BAY88-8223) was administered 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses (“standard dose”)

Arm title	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)

Arm description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 88 kBq/kg IV every 28 days for up to 6 doses (“high dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

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 dichloride (Xofigo, BAY88-8223) was administered 88 kBq/kg intravenously (IV) every 28 days for up to 6 doses (“high dose”)

Arm title	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)

Arm description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg IV every 28 days for up to 12 doses ("extended dose"). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

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 dichloride (Xofigo, BAY88-8223) was administered 55 kBq/kg intravenously (IV) every 28 days for up to 12 doses ("extended dose")

Number of subjects in period 1	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)
Started	130	130	131
Received Treatment	125	124	121
Completed	84	67	29
Not completed	46	63	102
Clinical progression	10	8	28
Consent withdrawn by subject	4	5	13
Never Treated	5	6	10
Physician decision	-	-	1
Logistical difficulties	1	1	1
Radiological progression	13	17	26
Adverse event, non-fatal	13	25	23
Safety outcome reached	-	1	-

Period 2

Period 2 title	Active follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No

Arm title	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)

Arm description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses ("standard dose"). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

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 dichloride (Xofigo, BAY88-8223) was administered 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses (“standard dose”)

Arm title	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)

Arm description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 88 kBq/kg IV every 28 days for up to 6 doses (“high dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

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 dichloride (Xofigo, BAY88-8223) was administered 88 kBq/kg intravenously (IV) every 28 days for up to 6 doses (“high dose”)

Arm title	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)

Arm description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg IV every 28 days for up to 12 doses (“extended dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

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 dichloride (Xofigo, BAY88-8223) was administered 55 kBq/kg intravenously (IV) every 28 days for up to 12 doses (“extended dose”)

Number of subjects in period 2	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)
Started	120	120	116
Completed	28	21	17
Not completed	92	99	99
Adverse event, serious fatal	83	82	87
Clinical progression	-	2	1
Consent withdrawn by subject	5	13	7
Other unspecified	2	-	1
Radiological progression	-	-	1
Deterioration of general condition	1	1	1
Lost to follow-up	1	1	1

Period 3

Period 3 title	Long-term follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)

Arm description:

Participants who were randomized in a 1:1:1 fashion received Xofigo (Radium-223 dichloride, BAY88-8223) 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses (“standard dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

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 dichloride (Xofigo, BAY88-8223) was administered 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses (“standard dose”)

Arm title	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)

Arm description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride 88 kBq/kg IV every 28 days for up to 6 doses (“high dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

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 dichloride (Xofigo, BAY88-8223) was administered 88 kBq/kg intravenously (IV) every 28 days for up to 6 doses ("high dose")

Arm title	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)

Arm description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride 55 kBq/kg IV every 28 days for up to 12 doses ("extended dose"). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

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 dichloride (Xofigo, BAY88-8223) was administered 55 kBq/kg intravenously (IV) every 28 days for up to 12 doses ("extended dose")

Number of subjects in period 3	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)
Started	28	21	17
Completed	0	0	0
Not completed	28	21	17
Adverse event, serious fatal	9	6	4
Consent withdrawn by subject	6	3	-
Other unspecified	6	3	5
Technical problems	-	-	1
Lost to follow-up	1	-	1
Entered the long-term follow-up study	6	9	6

Baseline characteristics

Reporting groups	
Reporting group title	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)
Reporting group description:	
Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses ("standard dose"). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.	
Reporting group title	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)
Reporting group description:	
Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 88 kBq/kg IV every 28 days for up to 6 doses ("high dose"). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.	
Reporting group title	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)
Reporting group description:	
Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg IV every 28 days for up to 12 doses ("extended dose"). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.	

Reporting group values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)
Number of subjects	130	130	131
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	70.6	70.9	70.0
standard deviation	± 8.6	± 8.3	± 8.1
Gender categorical Units: Subjects			
Female	0	0	0
Male	130	130	131

Race/Ethnicity Units: Subjects			
White	104	102	108
Black or African American	3	5	5
Asian	17	17	13
Not reported	6	6	5
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	3	6
Not Hispanic or Latino	125	124	120
Unknown or Not Reported	4	3	5
ECOG PS			
Eastern Cooperative Oncology Group Performance status (ECOG PS): 0-Fully active, able to carry on all pre-diseases performance without restriction, (Karnofsky 90-100); 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature,(Karnofsky 70-80) 2-Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60); 3-Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40); 4-Completely disabled.			
Units: Subjects			
ECOG PS=0	48	59	49
ECOG PS=1	78	67	77
ECOG PS=2	4	4	5
Extent of disease Units: Subjects			
Normal or abnormal because of benign bone disease	0	1	0
<6 metastases	19	22	19
6-20 metastases	52	53	52
>20 lesions but not a superscan	47	48	54
Superscan	12	6	6
Average Worst Pain Score (WPS)			
Brief Pain Short Form (BPI-SF) encompasses 4 different items to capture the variability of pain over time (pain at its "worst," "least," "average," and "now"). Only the worst pain score (WPS) in the last 24 hours was assessed (a visual analogic scale ranging 0-10, with 0 meaning "no pain" and 10 meaning "pain as bad as you can imagine"), and the mean score of the 7 days prior to the study visit or telephone contact was calculated and this value was recorded in the participant's reported outcome pain data. Actual number of participants analyzed in Arm A, B, C was 128, 128 and 122, respectively			
Units: scores on a scale			
arithmetic mean	3.6	3.3	3.4
standard deviation	± 2.6	± 2.5	± 2.6
Time from initial prostate cancer diagnosis to randomization Units: months			
median	58.9	72.9	67.1
full range (min-max)	2 to 285	7 to 279	8 to 396
Time from initial bone metastases diagnosis to randomization Units: months			
median	30.8	29.9	37.5
full range (min-max)	2 to 231	1 to 170	1 to 397
Time from most recent prostate cancer progression to randomization			
The last assessment collected prior to randomization was used as baseline value. If no assessment was done prior to randomization, then the assessment collected after randomization but prior to first dose was used as baseline. Number of analyzed reflect the participants with data available at baseline. Actual number of participants analyzed in Arm A was 129.			

Units: months			
median	1.4	1.4	1.3
full range (min-max)	0 to 8	0 to 9	0 to 10
Time from most recent bone metastases progression to randomization			
The last assessment collected prior to randomization was used as baseline value. If no assessment was done prior to randomization, then the assessment collected after randomization but prior to first dose was used as baseline. Number of analyzed reflect the participants with data available at baseline. Actual number of subjects analyzed in Arm A, B, C was 118, 119, and 121, respectively.			
Units: months			
median	2.3	2.8	1.9
full range (min-max)	0 to 34	0 to 93	0 to 41
Body Mass Index			
The last assessment collected prior to randomization was used as baseline value. If no assessment was done prior to randomization, then the assessment collected after randomization but prior to first dose was used as baseline. Number of analyzed reflect the participants with data available at baseline. Actual number of participants analyzed in Arm A, B, C was 126, 127, and 124, respectively.			
Units: kg/m^2			
arithmetic mean	28.4	28.0	29.1
standard deviation	± 5.2	± 5.2	± 5.4
Time from first bone metastases progression to most recent progression			
The last assessment collected prior to randomization was used as baseline value. If no assessment was done prior to randomization, then the assessment collected after randomization but prior to first dose was used as baseline. Number of analyzed reflect the participants with data available at baseline. Actual number of participants analyzed in Arm A, B, C was 118, 119, and 120, respectively.			
Units: months			
median	7.9	8.9	13.4
full range (min-max)	0 to 72	0 to 71	0 to 120

Reporting group values	Total		
Number of subjects	391		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	0		
Male	391		

Race/Ethnicity Units: Subjects			
White	314		
Black or African American	13		
Asian	47		
Not reported	17		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	10		
Not Hispanic or Latino	369		
Unknown or Not Reported	12		
ECOG PS			
Eastern Cooperative Oncology Group Performance status (ECOG PS): 0-Fully active, able to carry on all pre-diseases performance without restriction, (Karnofsky 90-100); 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature,(Karnofsky 70-80) 2-Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60); 3-Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40); 4-Completely disabled.			
Units: Subjects			
ECOG PS=0	156		
ECOG PS=1	222		
ECOG PS=2	13		
Extent of disease Units: Subjects			
Normal or abnormal because of benign bone disease	1		
<6 metastases	60		
6-20 metastases	157		
>20 lesions but not a superscan	149		
Superscan	24		
Average Worst Pain Score (WPS)			
Brief Pain Short Form (BPI-SF) encompasses 4 different items to capture the variability of pain over time (pain at its "worst," "least," "average," and "now"). Only the worst pain score (WPS) in the last 24 hours was assessed (a visual analogic scale ranging 0-10, with 0 meaning "no pain" and 10 meaning "pain as bad as you can imagine"), and the mean score of the 7 days prior to the study visit or telephone contact was calculated and this value was recorded in the participant's reported outcome pain data. Actual number of participants analyzed in Arm A, B, C was 128, 128 and 122, respectively			
Units: scores on a scale arithmetic mean standard deviation	- -		
Time from initial prostate cancer diagnosis to randomization Units: months median full range (min-max)	- -		
Time from initial bone metastases diagnosis to randomization Units: months median full range (min-max)	- -		
Time from most recent prostate cancer progression to randomization			
The last assessment collected prior to randomization was used as baseline value. If no assessment was done prior to randomization, then the assessment collected after randomization but prior to first dose was used as baseline. Number of analyzed reflect the participants with data available at baseline. Actual number of participants analyzed in Arm A was 129.			

Units: months median full range (min-max)	-		
Time from most recent bone metastases progression to randomization			
The last assessment collected prior to randomization was used as baseline value. If no assessment was done prior to randomization, then the assessment collected after randomization but prior to first dose was used as baseline. Number of analyzed reflect the participants with data available at baseline. Actual number of subjects analyzed in Arm A, B, C was 118, 119, and 121, respectively.			
Units: months median full range (min-max)	-		
Body Mass Index			
The last assessment collected prior to randomization was used as baseline value. If no assessment was done prior to randomization, then the assessment collected after randomization but prior to first dose was used as baseline. Number of analyzed reflect the participants with data available at baseline. Actual number of participants analyzed in Arm A, B, C was 126, 127, and 124, respectively.			
Units: kg/m^2 arithmetic mean standard deviation	-		
Time from first bone metastases progression to most recent progression			
The last assessment collected prior to randomization was used as baseline value. If no assessment was done prior to randomization, then the assessment collected after randomization but prior to first dose was used as baseline. Number of analyzed reflect the participants with data available at baseline. Actual number of participants analyzed in Arm A, B, C was 118, 119, and 120, respectively.			
Units: months median full range (min-max)	-		

End points

End points reporting groups

Reporting group title	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses (“standard dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

Reporting group title	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 88 kBq/kg IV every 28 days for up to 6 doses (“high dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

Reporting group title	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg IV every 28 days for up to 12 doses (“extended dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

Reporting group title	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses ("standard dose"). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

Reporting group title	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 88 kBq/kg IV every 28 days for up to 6 doses (“high dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

Reporting group title	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg IV every 28 days for up to 12 doses (“extended dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

Reporting group title	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Xofigo (Radium-223 dichloride, BAY88-8223) 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses (“standard dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

Reporting group title	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride 88 kBq/kg IV every 28 days for up to 6 doses (“high dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

Reporting group title	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride 55 kBq/kg IV every 28 days for up to 12 doses (“extended dose”). Participants who discontinued study treatment and who did not have an SSE entered an active follow-up period with clinic visits. Participants from the treatment period or the active follow-up period with clinic visits who could no longer travel entered an active follow-up period without clinic visits. All study participants eligible for further follow-up were either in this study or in a separate long term follow-up study for up to 7 years.

Subject analysis set title	Pooled Radium-223 55 kBq/kg (Arms A and C)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Arms A and C, participants who were randomized in a 1:1:1 fashion received radium-223 dichloride 55 kBq/kg IV every 28 days for up to 6 and 12 doses, respectively.

Primary: Number of Participants with an Event Defining SSE Free Survival - High dose vs. Standard dose

End point title	Number of Participants with an Event Defining SSE Free Survival - High dose vs. Standard dose[1][2]

End point description:

Symptomatic skeletal event (SSE) free survival is based on the following events: the use of external beam radiotherapy (EBRT) to relieve skeletal symptoms; the occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral); the occurrence of spinal cord compression; a tumor related orthopedic surgical intervention, and death. In this evaluation - comparison 1, SSE-FS following randomization is defined in ITT participants as the time from randomization to an SSE or death, whichever occurs first.

End point type	Primary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis in this end point is descriptive, comparison analysis results are presented in following end point.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	261		
Units: Count of Participants	85	118		

Statistical analyses

No statistical analyses for this end point

Primary: Symptomatic Skeletal Event-Free Survival - High dose vs. Standard dose

End point title	Symptomatic Skeletal Event-Free Survival - High dose vs. Standard dose[3]

End point description:

In this evaluation - comparison 1, SSE-FS following randomization is defined in ITT participants as the time from randomization to an SSE or death, whichever occurs first.

End point type	Primary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	261		
Units: months				
median (confidence interval 80%)	12.9 (10.9 to 14.8)	12.3 (10.3 to 13.5)		

Statistical analyses

Statistical analysis title	Arm B / Arm (A+C)
Comparison groups	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B) v Pooled Radium-223 55 kBq/kg (Arms A and C)
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7047
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.057
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.878
upper limit	1.272

Primary: Number of Participants with an Event defining SSE Free Survival - Extended dose vs. Standard dose

End point title	Number of Participants with an Event defining SSE Free

	Survival - Extended dose vs. Standard dose[4][5]

End point description:

Symptomatic skeletal event (SSE) free survival is based on the following events: the use of external beam radiotherapy (EBRT) to relieve skeletal symptoms; the occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral); the occurrence of spinal cord compression; a tumor related orthopedic surgical intervention, and death. In this evaluation - Comparison 2, SSE-FS from 6th dose is defined in W24 participants as the time from Week 24 baseline (the 6th dose date) to an SSE or death, whichever occurs first.
Week 24 (W24): All ITT participants in Arm A (standard dose) and Arm C (extended dosing) treated with radium-223 dichloride and eligible for further treatment at W24 (i.e., 7th injection). All participants who received 6 doses from Arm A and participants who received >=6 doses from Arm C were included .

End point type	Primary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis in this end point is descriptive, comparison analysis results are presented in following end point.
[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84[6]	69[7]		
Units: participants	41	40		

Notes:

[6] - Week 24: participants who received 6 doses from Arm A and who received >=6 doses from Arm C.

[7] - Week 24: participants who received 6 doses from Arm A and who received >=6 doses from Arm C.

Statistical analyses

No statistical analyses for this end point

Primary: Symptomatic Skeletal Event-Free Survival - Extended dose vs. Standard dose

End point title	Symptomatic Skeletal Event-Free Survival - Extended dose vs. Standard dose[8]

End point description:

In this evaluation - Comparison 2, SSE-FS from 6th dose is defined in W24 participants as the time from Week 24 baseline (the 6th dose date) to an SSE or death, whichever occurs first.

End point type	Primary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	69		
Units: months				
median (confidence interval 80%)	13.2 (9.2 to 18.1)	10.8 (8.1 to 13.8)		

Statistical analyses

Statistical analysis title	Arm C /Arm A
Comparison groups	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A) v Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3134
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.939
upper limit	1.69

Primary: Number of Participants with an Event Defining SSE Free Survival - Three Dose Groups As Randomized

End point title	Number of Participants with an Event Defining SSE Free Survival - Three Dose Groups As Randomized[9]

End point description:

Symptomatic skeletal event (SSE) free survival is based on the following events: the use of external beam radiotherapy (EBRT) to relieve skeletal symptoms; the occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral); the occurrence of spinal cord compression; a tumor related orthopedic surgical intervention, and death.

End point type	Primary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis in this end point is descriptive.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: participants	80	85	92	

Statistical analyses

No statistical analyses for this end point

Primary: Symptomatic Skeletal Event Free Survival - Three Dose Groups As Randomized

End point title	Symptomatic Skeletal Event Free Survival - Three Dose Groups As Randomized[10]

End point description:

Symptomatic skeletal event (SSE) is defined as follows: The use of external beam radiotherapy (EBRT) to relieve skeletal symptoms; The occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral); The occurrence of spinal cord compression; A tumor related orthopedic surgical intervention.

End point type	Primary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis in this end point is descriptive.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: months				
median (confidence interval 80%)	13.1 (11.0 to 14.6)	12.9 (10.9 to 14.8)	9.6 (9.0 to 10.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Overall Survival Event - High dose vs. Standard dose

End point title	Number of Participants with an Overall Survival Event - High dose vs. Standard dose[11]

End point description:

Overall survival was defined as the time in days from the applicable start date to the date of death due to any cause. Participants who were still alive or who were lost to survival follow-up as of database cut-

off date were to be censored at the last known alive date on or prior to database cut-off date.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	261[12]		
Units: participants	89	106		

Notes:

[12] - Data from Arm C are truncated at 7th dose date when pooling with Arm A.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - High dose vs. Standard dose

End point title	Overall Survival - High dose vs. Standard dose[13]

End point description:

Overall survival was defined as the time in days from the applicable start date to the date of death due to any cause. Participants who were still alive or who were lost to survival follow-up as of database cut-off date were to be censored at the last known alive date on or prior to database cut-off date.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	261[14]		
Units: months				
median (confidence interval 80%)	16.0 (14.7 to 17.2)	14.9 (13.7 to 16.7)		

Notes:

[14] - Data from Arm C are truncated at 7th dose date when pooling with Arm A.

Statistical analyses

Statistical analysis title	Arm B/Arm (A+C)
Comparison groups	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B) v Pooled Radium-223 55 kBq/kg (Arms A and C)
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6205
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.075
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.892
upper limit	1.297

Secondary: Number of Participants with an Overall survival event - Extended dose vs. Standard dose

End point title	Number of Participants with an Overall survival event - Extended dose vs. Standard dose[15]

End point description:

Overall survival was defined as the time in days from the applicable start date to the date of death due to any cause. Participants who were still alive or who were lost to survival follow-up as of database cut-off date were to be censored at the last known alive date on or prior to database cut-off date.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84[16]	69[17]		
Units: participants	43	38		

Notes:

[16] - Week 24 (W24)

[17] - Week 24 (W24)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival - Extended dose vs. Standard dose

End point title	Overall survival - Extended dose vs. Standard dose[18]

End point description:

Overall survival was defined as the time in days from the applicable start date to the date of death due to any cause. Participants who were still alive or who were lost to survival follow-up as of database cut-off date were to be censored at the last known alive date on or prior to database cut-off date.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84[19]	69[20]		
Units: months				
median (full range (min-max))	16.5 (14.0 to 19.9)	15.2 (14.0 to 19.0)		

Notes:

[19] - Week 24 (W24)

[20] - Week 24 (W24)

Statistical analyses

Statistical analysis title	Arm C/Arm A
Comparison groups	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A) v Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9958
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.999
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.744
upper limit	1.341

Secondary: Number of Participants with an Overall Survival - Three Dose Groups As Randomized

End point title	Number of Participants with an Overall Survival - Three Dose Groups As Randomized

End point description:

Overall survival was defined as the time in days from the applicable start date to the date of death due to any cause. Participants who were still alive or who were lost to survival follow-up as of database cut-off date were to be censored at the last known alive date on or prior to database cut-off date.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: participants	83	89	93	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Event - Three Dose Groups as Randomized

End point title	Overall Survival Event - Three Dose Groups as Randomized

End point description:

Overall survival was defined as the time in days from the applicable start date to the date of death due to any cause. Participants who were still alive or who were lost to survival follow-up as of database cut-off date were to be censored at the last known alive date on or prior to database cut-off date.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: months				
median (confidence interval 80%)	15.8 (14.3 to 18.1)	16.0 (14.7 to 17.2)	14.4 (12.1 to 16.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with First Symptomatic Skeletal Event - High dose vs. Standard dose

End point title	Number of Participants with First Symptomatic Skeletal Event - High dose vs. Standard dose[21]

End point description:

Symptomatic skeletal event (SSE) is defined as follows: The use of external beam radiotherapy (EBRT) to relieve skeletal symptoms; The occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral); The occurrence of spinal cord compression; A tumor related orthopedic surgical intervention.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	261[22]		
Units: participants	42	62		

Notes:

[22] - Data from Arm C are truncated at 7th dose date when pooling with Arm A.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Symptomatic Skeletal Event - High dose vs. Standard dose

End point title	Time to First Symptomatic Skeletal Event - High dose vs. Standard dose[23]

End point description:

Time to first SSE is defined as the time in days from the applicable start date to the first SSE on or following the start date.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130[24]	261[25]		
Units: months				
median (confidence interval 80%)	24.1 (18.0 to 99999)	26.3 (26.3 to 99999)		

Notes:

[24] - "99999" entered below stands for "NA" because of no sufficient events observed for calculation.

[25] - "99999" entered below stands for "NA" because of no sufficient events observed for calculation.

Statistical analyses

Statistical analysis title	Arm B/Arm (A+C)
Comparison groups	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B) v Pooled Radium-223 55 kBq/kg (Arms A and C)
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7461
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.068
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.823
upper limit	1.385

Secondary: Number of Participants with First Symptomatic Skeletal Event - Extended dose vs. Standard dose

End point title	Number of Participants with First Symptomatic Skeletal Event - Extended dose vs. Standard dose[26]

End point description:

Symptomatic skeletal event (SSE) is defined as follows: The use of external beam radiotherapy (EBRT) to relieve skeletal symptoms; The occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral); The occurrence of spinal cord compression; A tumor related orthopedic surgical intervention.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84[27]	69[28]		
Units: participants	19	25		

Notes:

[27] - Week 24 (W24)

[28] - Week 24 (W24)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Symptomatic Skeletal Event - Extended dose vs. Standard dose

End point title	Time to First Symptomatic Skeletal Event - Extended dose vs. Standard dose[29]

End point description:

Time to first SSE is defined as the time in days from the applicable start date to the first SSE on or following the start date.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84[30]	69		
Units: months				
median (confidence interval 80%)	99999 (21.2 to 99999)	19.5 (12.3 to 23.4)		

Notes:

[30] - "99999" entered below stands for “NA” because of no sufficient events observed for calculation.

Statistical analyses

Statistical analysis title	Arm C/Arm A
Comparison groups	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A) v Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.155
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.549
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.041
upper limit	2.306

Secondary: Number of Participants with First Symptomatic Skeletal Event - Three Dose Groups as Randomized

End point title	Number of Participants with First Symptomatic Skeletal Event - Three Dose Groups as Randomized

End point description:

Symptomatic skeletal event (SSE) is defined as follows: The use of external beam radiotherapy (EBRT) to relieve skeletal symptoms; The occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral); The occurrence of spinal cord compression; A tumor related orthopedic surgical intervention.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: participants	37	42	48	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Symptomatic Skeletal Event - Three Dose Groups as Randomized

End point title	Time to First Symptomatic Skeletal Event - Three Dose Groups as Randomized

End point description:

Time to first SSE is defined as the time in days from the applicable start date to the first SSE on or following the start date.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130[31]	130[32]	131	
Units: months				
median (confidence interval 80%)	99999 (26.3 to 99999)	24.1 (18.0 to 99999)	18.8 (15.1 to 25.6)	

Notes:

[31] - "99999" entered below stands for "NA" because of no sufficient events observed for calculation.

[32] - "99999" entered below stands for "NA" because of no sufficient events observed for calculation.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Radiological Progression Event-Free – High dose vs. Standard dose

End point title	Number of Participants With a Radiological Progression Event-Free – High dose vs. Standard dose[33]

End point description:

Radiological progression of soft tissue disease is determined according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 based on Magnetic resonance imaging (MRI) or computed tomography (CT) scans. Radiological progression of osseous disease is determined according to adapted PCWG2 criteria based on whole body technetium-99 bone scans. Radiological bone progression is determined if at least one of the following criteria is met: The first bone scan with ≥2 new lesions compared to baseline is observed <12 weeks from randomization and is confirmed by a second bone scan taken ≥6 weeks later showing ≥2 additional new lesions (a total of ≥4 new lesions compared to baseline); or The first bone scan with ≥2 new lesions compared to baseline is observed ≥12 weeks from randomization and the new lesions are verified on the next bone scan ≥6 weeks later (a total of ≥2 new lesions compared to baseline).

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	261		
Units: participants	77	141		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiological Progression Free Survival – High dose vs. Standard dose

End point title	Radiological Progression Free Survival – High dose vs. Standard dose[34]

End point description:

Radiological progression free survival is defined as the time in days from the applicable start date to the date of subsequent radiological disease progression or death from any cause (if death occurs before such progression). Participants not experiencing death or radiological disease progression as of database cut-off were censored at the last radiological disease progression assessment.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	261		
Units: months				
median (confidence interval 80%)	7.5 (5.9 to 8.6)	6.0 (5.2 to 6.2)		

Statistical analyses

Statistical analysis title	Arm B/Arm (A+C)
Comparison groups	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B) v Pooled Radium-223 55 kBq/kg (Arms A and C)

Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8284
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.969
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.805
upper limit	1.167

Secondary: Number of Participants With a Radiological Progression Event-Free – Extended dose vs. Standard dose

End point title	Number of Participants With a Radiological Progression Event-Free – Extended dose vs. Standard dose[35]

End point description:

Radiological progression of soft tissue disease is determined according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 based on Magnetic resonance imaging (MRI) or Computed tomography (CT) scans. Radiological progression of osseous disease is determined according to adapted PCWG2 criteria based on whole body technetium-99 bone scans.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84[36]	47[37]		
Units: participants	49	47		

Notes:

[36] - Baseline is randomization date

[37] - Baseline is randomization date

Statistical analyses

No statistical analyses for this end point

Secondary: Radiological Progression Free Survival - Extended dose vs. Standard dose

End point title	Radiological Progression Free Survival - Extended dose vs. Standard dose[38]

End point description:

Radiological progression free survival is defined as the time in days from the applicable start date to the date of subsequent radiological disease progression or death from any cause (if death occurs before such progression). Participants not experiencing death or radiological disease progression as of database cut-off were censored at the last radiological disease progression assessment.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84[39]	69[40]		
Units: months				
median (confidence interval 80%)	8.9 (6.3 to 11.8)	9.0 (7.5 to 9.6)		

Notes:

[39] - Baseline is randomization date

[40] - Baseline is randomization date

Statistical analyses

Statistical analysis title	Arm C/Arm A
Comparison groups	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C) v Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7896
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.059
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.804
upper limit	1.396

Secondary: Number of Participants with a Radiological Progression Event-Free - Three Dose Groups as Randomized

End point title	Number of Participants with a Radiological Progression Event-Free - Three Dose Groups as Randomized

End point description:

Radiological progression of soft tissue disease is determined according to Response Evaluation Criteria in

Solid Tumors (RECIST) 1.1 based on Magnetic resonance imaging (MRI) or Computed tomography (CT) scans. Radiological progression of osseous disease is determined according to adapted Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria based on whole body technetium-99 bone scans.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: participants	77	77	90	

Statistical analyses

No statistical analyses for this end point

Secondary: Radiological Progression Free Survival - Three Dose Groups as Randomized

End point title	Radiological Progression Free Survival - Three Dose Groups as Randomized

End point description:

Radiological progression free survival is defined as the time in days from the applicable start date to the date of subsequent radiological disease progression or death from any cause (if death occurs before such progression). Participants not experiencing death or radiological disease progression as of database cut-off were censored at the last radiological disease progression assessment.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: months				
median (confidence interval 80%)	6.3 (5.1 to 7.2)	7.5 (5.9 to 8.6)	6.1 (5.2 to 6.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Radiological Progression Event – High dose vs. Standard dose

End point title	Number of Participants With a Radiological Progression Event – High dose vs. Standard dose[41]

End point description:

Radiological progression of soft tissue disease is determined according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 based on Magnetic resonance imaging (MRI) or Computed tomography (CT) scans. Radiological progression of osseous disease is determined according to adapted Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria based on whole body technetium-99 bone scans.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	261		
Units: participants	63	115		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Radiological Progression – High dose vs. Standard dose

End point title	Time to Radiological Progression – High dose vs. Standard

End point description:

Time to radiological progression is defined as the time in days from the applicable start date to the date of subsequent radiological progression. Participants without radiological progression as of database cut-off date, whether or not surviving, were censored at the last radiological progression assessment.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	261[43]		
Units: months				
median (confidence interval 80%)	8.7 (6.2 to 9.7)	6.2 (6.0 to 6.6)		

Notes:

[43] - Data from Arm C are truncated at 7th dose date when pooling with Arm A.

Statistical analyses

Statistical analysis title	Arm B/Arm (A+C)
Comparison groups	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B) v Pooled Radium-223 55 kBq/kg (Arms A and C)
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9274
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.986
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.803
upper limit	1.21

Secondary: Number of Participants With a Radiological Progression Event – Extended dose vs. Standard dose

End point title	Number of Participants With a Radiological Progression Event – Extended dose vs. Standard dose[44]

End point description:

Radiological progression free survival is defined as the time in days from the applicable start date to the date of subsequent radiological disease progression or death from any cause (if death occurs before such progression). Participants not experiencing death or radiological disease progression as of database cut-off were censored at the last radiological disease progression assessment.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84[45]	69[46]		
Units: participants	43	43		

Notes:

[45] - Week 24 (W24)

[46] - Week 24 (W24)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Radiological Progression - Extended dose vs. Standard dose

End point title	Time to Radiological Progression - Extended dose vs. Standard dose[47]

End point description:

Time to radiological progression is defined as the time in days from the applicable start date to the date of subsequent radiological progression. Participants without radiological progression as of database cut-off date, whether or not surviving, were censored at the last radiological progression assessment.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	69		
Units: months				
median (confidence interval 80%)	8.9 (6.3 to 14.6)	9.0 (7.2 to 10.2)		

Statistical analyses

Statistical analysis title	Arm C/Arm A
Comparison groups	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C) v Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5754
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.134
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.85
upper limit	1.514

Secondary: Number of Participants with a Radiological Progression event - Three Dose Groups as Randomized

End point title	Number of Participants with a Radiological Progression event - Three Dose Groups as Randomized

End point description:

Radiological progression free survival is defined as the time in days from the applicable start date to the date of subsequent radiological disease progression or death from any cause (if death occurs before such progression). Participants not experiencing death or radiological disease progression as of database cut-off were censored at the last radiological disease progression assessment.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: participants	66	63	67	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Radiological Progression - Three Dose Groups as Randomized

End point title	Time to Radiological Progression - Three Dose Groups as Randomized

End point description:

Time to radiological progression is defined as the time in days from the applicable start date to the date of subsequent radiological progression. Participants without radiological progression as of database cut-off date, whether or not surviving, were censored at the last radiological progression assessment.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: months				
median (confidence interval 80%)	6.2 (5.9 to 7.1)	8.7 (6.2 to 9.7)	6.6 (6.0 to 8.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Timepoint Pain Improvement Rate - Three Dose Groups as Randomized

End point title	Timepoint Pain Improvement Rate - Three Dose Groups as Randomized

End point description:

Time point pain improvement rate is defined as the proportion of participants with a 30% and 2-point decrease in Worst pain score (WPS) from baseline over 2 consecutive assessment periods conducted at least 4 weeks apart among participants with a WPS score ≥ 4 at baseline.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: percentage				
number (confidence interval 80%)				
Week 12	16.7 (10.1 to 25.7)	16.0 (9.5 to 24.7)	18.6 (11.1 to 28.5)	
Overall (confirmed)	27.1 (18.7 to 37.0)	26.0 (17.9 to 35.6)	37.2 (27.3 to 48.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Timepoint Pain Improvement Rate - Extended dose vs. Standard dose

End point title	Timepoint Pain Improvement Rate - Extended dose vs. Standard dose[48]

End point description:

Timepoint pain improvement rate is defined as the proportion of participants with a 30% and 2-point decrease in Worst pain score (WPS) from baseline over 2 consecutive assessment periods conducted at least 4 weeks apart among participants with a WPS score ≥ 4 at baseline.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: percentage				
number (confidence interval 80%)				
Week 12	31.8 (18.7 to 47.7)	30.0 (16.6 to 46.7)		
Overall (confirmed)	40.9 (26.4 to 56.8)	55.0 (38.5 to 70.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Pain Progression Event – High dose vs. Standard dose

End point title	Number of Participants With a Pain Progression Event – High dose vs. Standard dose[49]

End point description:

Participants were divided in 3 groups according to baseline pain evaluation: asymptomatic subjects (WPS 0 to < 1 at baseline); mildly symptomatic subjects (WPS 1-3 at baseline); and symptomatic subjects with WPS > 3 and ≤ 7 at baseline). Pain progression was defined as the occurrence of a pain increase of 2 or more points in the average (i.e., average of 7-day assessments) "worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart. Participants with insufficient applicable baseline assessments or without adequate post-baseline assessments were to be censored at the applicable baseline date.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient

randomization)

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	113	218[50]		
Units: participants	31	68		

Notes:

[50] - Data from Arm C are truncated at 7th dose date when pooling with Arm A.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Progression – High dose vs. Standard dose

End point title	Time to Pain Progression – High dose vs. Standard dose[51]

End point description:

The time to pain progression is defined for each applicable baseline for applicable participants as the time (in days) from the respective baseline until occurrence of the first post-baseline pain progression event.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm A and C were pooled together as 'standard dose' group based on pre-specified pooling rule.

End point values	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Pooled Radium-223 55 kBq/kg (Arms A and C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	113[52]	218[53]		
Units: months				
median (confidence interval 80%)	99999 (9.4 to 99999)	99999 (8.6 to 99999)		

Notes:

[52] - "99999" entered below stands for “NA” because of no sufficient events observed for calculation.

[53] - "99999" entered below stands for “NA” because of no sufficient events observed for calculation.

Statistical analyses

Statistical analysis title	Arm B/Arm (A+C)
Comparison groups	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B) v Pooled

	Radium-223 55 kBq/kg (Arms A and C)
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6214
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.898
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.678
upper limit	1.188

Secondary: Number of Participants With a Pain Progression Event – Extended dose vs. Standard dose

End point title	Number of Participants With a Pain Progression Event – Extended dose vs. Standard dose[54]

End point description:

Pain progression is defined for each baseline in participants evaluable for pain progression at the applicable baseline, i.e., participants with a WPS of ≤ 7 at the respective baseline assessment.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[55]	65[56]		
Units: participants	10	15		

Notes:

[55] - Week 24 (W24)

[56] - Week 24 (W24)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Progression - Extended dose vs. Standard dose

End point title	Time to Pain Progression - Extended dose vs. Standard dose[57]

End point description:

The time to pain progression is defined for each applicable baseline for applicable participants as the time (in days) from the respective baseline until occurrence of the first post-baseline pain progression

event.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The comparison was performed between "standard dose" (arm A) vs. "extended dose" (Arm C) only, the study was not designed for a comparison between the 3 arms.

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[58]	65[59]		
Units: months				
median (confidence interval 80%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[58] - "99999" entered below stands for "NA" because of no sufficient events observed for calculation.

[59] - "99999" entered below stands for "NA" because of no sufficient events observed for calculation.

Statistical analyses

Statistical analysis title	Arm C/Arm A
Comparison groups	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A) v Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7214
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.863
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.505
upper limit	1.475

Secondary: Number of Participants with a Pain Progression event - Three Dose Groups as Randomized

End point title	Number of Participants with a Pain Progression event - Three Dose Groups as Randomized

End point description:

Pain progression is defined for each baseline in participants evaluable for pain progression at the applicable baseline, i.e., participants with a WPS of ≤ 7 at the respective baseline assessment.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	113	108	
Units: participants	32	31	46	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Progression - Three Dose Groups as Randomized

End point title	Time to Pain Progression - Three Dose Groups as Randomized

End point description:

The time to pain progression is defined for each applicable baseline for applicable participants as the time (in days) from the respective baseline until occurrence of the first post-baseline pain progression event.

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110[60]	113[61]	108	
Units: months				
median (confidence interval 80%)	99999 (8.9 to 99999)	99999 (9.4 to 99999)	10.1 (8.8 to 11.8)	

Notes:

[60] - "99999" entered below stands for "NA" because of no sufficient events observed for calculation.

[61] - "99999" entered below stands for "NA" because of no sufficient events observed for calculation.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent Adverse Events

End point title	Number of Participants with Treatment-Emergent Adverse

	Events

End point description:

Treatment-emergent adverse events are events starting or worsening from the initiation of treatment until 30 days after the last administration of radium-223 dichloride. The intensity of an AE is classified according to the grades specified by the National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE).

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124[62]	121[63]	125[64]	
Units: participants				
Any TEAE	118	119	116	
Grade 1	23	20	18	
Grade 2	52	40	34	
Grade 3	38	46	49	
Grade 4	4	11	11	
Grade 5	1	2	4	
Serious	25	36	37	
Any drug-related TEAE	73	73	57	

Notes:

[62] - Safety Analysis Set

[63] - Safety Analysis Set

[64] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Change in Analgesic Use from Baseline to Worst Status Post-Baseline

End point title	Number of Participants with Change in Analgesic Use from Baseline to Worst Status Post-Baseline

End point description:

Analgesic use in this study were captured via two methods: Analgesic concomitant medication case report form, where the physician records the analgesic medication prescribed to manage pain; 24 hour analgesic consumption case report form, in which all analgesic medication taken in the last 24 hours

End point type	Secondary

End point timeframe:

From randomization to 135 SSE-FS events have been observed in comparison 1 or 75 SSE-FS events observed in comparison 2, whichever occurred last (approximately 36 months from first patient randomization)

End point values	Radium-223 dichloride 55 kBq/kg, 6 doses (Arm A)	Radium-223 dichloride 88 kBq/kg, 6 doses (Arm B)	Radium-223 dichloride 55 kBq/kg, 12 doses (Arm C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	130	131	
Units: participants				
Strong Opioid - No Change	22	27	26	
From Strong Opioid to Weak Opioid	1	0	2	
From Strong Opioid to No analgesic or Non-opioid	18	9	13	
From Strong Opioid to Missing	2	0	4	
From No analgesic or Non-opioid to Strong Opioid	24	26	25	
From No analgesic or Non-opioid to Weak Opioid	5	8	12	
No analgesic or Non-opioid - No Change	46	41	30	
From No analgesic or Non-opioid to Missing	5	5	5	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From starting of study medication over a period of approximately 3 years since first participant was enrolled.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Radium-223 55 kBq/kg Arm A (6 doses)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg intravenously (IV) every 28 days for up to 6 doses (“standard dose”).

Reporting group title	Radium-223 88 kBq/kg Arm B (6 doses)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 88 kBq/kg IV every 28 days for up to 6 doses (“high dose”).

Reporting group title	Radium-223 55 kBq/kg Arm C (12 doses)

Reporting group description:

Participants who were randomized in a 1:1:1 fashion received Radium-223 dichloride (Xofigo, BAY88-8223) 55 kBq/kg IV every 28 days for up to 12 doses (“extended dose”).

Serious adverse events	Radium-223 55 kBq/kg Arm A (6 doses)	Radium-223 88 kBq/kg Arm B (6 doses)	Radium-223 55 kBq/kg Arm C (12 doses)
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 125 (20.00%)	36 / 124 (29.03%)	37 / 121 (30.58%)
number of deaths (all causes)	98	100	102
number of deaths resulting from adverse events	1	2	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nasal cavity cancer			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 125 (0.80%)	1 / 124 (0.81%)	0 / 121 (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
General physical health deterioration			
subjects affected / exposed	2 / 125 (1.60%)	2 / 124 (1.61%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Cystitis radiation			

subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Traumatic fracture			
subjects affected / exposed	1 / 125 (0.80%)	1 / 124 (0.81%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract stoma complication			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute coronary syndrome			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
Headache			

subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IIIrd nerve paralysis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
Neuralgia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	0 / 121 (0.00%)
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 cord compression			
subjects affected / exposed	1 / 125 (0.80%)	6 / 124 (4.84%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 1	0 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal nerve disorder			

subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 125 (2.40%)	6 / 124 (4.84%)	4 / 121 (3.31%)
occurrences causally related to treatment / all	7 / 7	22 / 24	9 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 125 (0.00%)	3 / 124 (2.42%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Leukopenia			
subjects affected / exposed	0 / 125 (0.00%)	2 / 124 (1.61%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	13 / 13	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 125 (0.80%)	1 / 124 (0.81%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	2 / 125 (1.60%)	0 / 124 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 125 (0.00%)	3 / 124 (2.42%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 0	24 / 28	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental caries			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	3 / 121 (2.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			

subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
Back pain			
subjects affected / exposed	0 / 125 (0.00%)	2 / 124 (1.61%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	3 / 125 (2.40%)	1 / 124 (0.81%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coccydynia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
Muscular weakness			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			

subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
Pathological fracture			
subjects affected / exposed	1 / 125 (0.80%)	1 / 124 (0.81%)	3 / 121 (2.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	0 / 121 (0.00%)
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			
Gastroenteritis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	2 / 121 (1.65%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	2 / 125 (1.60%)	0 / 124 (0.00%)	0 / 121 (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
Urinary tract infection			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Enterocolitis infectious			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
Soft tissue infection			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (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
Metabolism and nutrition disorders			
Alcohol intolerance			

subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 124 (0.81%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 124 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 124 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 55 kBq/kg Arm A (6 doses)	Radium-223 88 kBq/kg Arm B (6 doses)	Radium-223 55 kBq/kg Arm C (12 doses)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 125 (87.20%)	111 / 124 (89.52%)	111 / 121 (91.74%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	4 / 125 (3.20%)	9 / 124 (7.26%)	3 / 121 (2.48%)
occurrences (all)	6	22	11
Weight decreased			
subjects affected / exposed	12 / 125 (9.60%)	6 / 124 (4.84%)	19 / 121 (15.70%)
occurrences (all)	17	7	24
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 125 (2.40%)	9 / 124 (7.26%)	4 / 121 (3.31%)
occurrences (all)	5	14	4
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 125 (4.80%)	5 / 124 (4.03%)	7 / 121 (5.79%)
occurrences (all)	7	9	17
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 125 (2.40%)	3 / 124 (2.42%)	8 / 121 (6.61%)
occurrences (all)	3	3	10
Headache			
subjects affected / exposed	7 / 125 (5.60%)	6 / 124 (4.84%)	6 / 121 (4.96%)
occurrences (all)	8	7	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	29 / 125 (23.20%)	33 / 124 (26.61%)	30 / 121 (24.79%)
occurrences (all)	64	69	79
Neutropenia			
subjects affected / exposed	2 / 125 (1.60%)	10 / 124 (8.06%)	5 / 121 (4.13%)
occurrences (all)	7	21	16
Thrombocytopenia			
subjects affected / exposed	7 / 125 (5.60%)	10 / 124 (8.06%)	10 / 121 (8.26%)
occurrences (all)	14	26	33
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	12 / 125 (9.60%)	9 / 124 (7.26%)	17 / 121 (14.05%)
occurrences (all)	15	11	25
Fatigue			
subjects affected / exposed	39 / 125 (31.20%)	37 / 124 (29.84%)	35 / 121 (28.93%)
occurrences (all)	58	46	49
Oedema peripheral			
subjects affected / exposed	9 / 125 (7.20%)	6 / 124 (4.84%)	7 / 121 (5.79%)
occurrences (all)	10	6	7
Pyrexia			
subjects affected / exposed	4 / 125 (3.20%)	9 / 124 (7.26%)	5 / 121 (4.13%)
occurrences (all)	4	9	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 125 (4.00%)	3 / 124 (2.42%)	10 / 121 (8.26%)
occurrences (all)	5	3	12
Constipation			
subjects affected / exposed	21 / 125 (16.80%)	10 / 124 (8.06%)	18 / 121 (14.88%)
occurrences (all)	27	11	20
Diarrhoea			
subjects affected / exposed	26 / 125 (20.80%)	28 / 124 (22.58%)	26 / 121 (21.49%)
occurrences (all)	34	39	32
Nausea			
subjects affected / exposed	31 / 125 (24.80%)	29 / 124 (23.39%)	28 / 121 (23.14%)
occurrences (all)	38	33	39
Vomiting			
subjects affected / exposed	12 / 125 (9.60%)	15 / 124 (12.10%)	17 / 121 (14.05%)
occurrences (all)	16	19	22
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 125 (2.40%)	4 / 124 (3.23%)	7 / 121 (5.79%)
occurrences (all)	5	4	7
Dyspnoea			
subjects affected / exposed	8 / 125 (6.40%)	4 / 124 (3.23%)	7 / 121 (5.79%)
occurrences (all)	8	4	7
Psychiatric disorders			

Depression			
subjects affected / exposed	4 / 125 (3.20%)	1 / 124 (0.81%)	7 / 121 (5.79%)
occurrences (all)	5	1	7
Insomnia			
subjects affected / exposed	9 / 125 (7.20%)	6 / 124 (4.84%)	5 / 121 (4.13%)
occurrences (all)	9	7	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 125 (16.00%)	17 / 124 (13.71%)	19 / 121 (15.70%)
occurrences (all)	26	22	24
Back pain			
subjects affected / exposed	20 / 125 (16.00%)	18 / 124 (14.52%)	24 / 121 (19.83%)
occurrences (all)	25	19	29
Bone pain			
subjects affected / exposed	23 / 125 (18.40%)	19 / 124 (15.32%)	27 / 121 (22.31%)
occurrences (all)	26	21	32
Muscular weakness			
subjects affected / exposed	6 / 125 (4.80%)	8 / 124 (6.45%)	2 / 121 (1.65%)
occurrences (all)	8	8	2
Musculoskeletal pain			
subjects affected / exposed	9 / 125 (7.20%)	7 / 124 (5.65%)	11 / 121 (9.09%)
occurrences (all)	11	7	12
Myalgia			
subjects affected / exposed	7 / 125 (5.60%)	4 / 124 (3.23%)	4 / 121 (3.31%)
occurrences (all)	9	4	4
Pain in extremity			
subjects affected / exposed	13 / 125 (10.40%)	9 / 124 (7.26%)	12 / 121 (9.92%)
occurrences (all)	15	10	13
Pathological fracture			
subjects affected / exposed	2 / 125 (1.60%)	4 / 124 (3.23%)	7 / 121 (5.79%)
occurrences (all)	2	4	9
Musculoskeletal chest pain			
subjects affected / exposed	11 / 125 (8.80%)	5 / 124 (4.03%)	8 / 121 (6.61%)
occurrences (all)	15	7	9
Spinal pain			

subjects affected / exposed	4 / 125 (3.20%)	1 / 124 (0.81%)	7 / 121 (5.79%)
occurrences (all)	7	1	12
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 125 (1.60%)	7 / 124 (5.65%)	2 / 121 (1.65%)
occurrences (all)	2	7	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	31 / 125 (24.80%)	24 / 124 (19.35%)	26 / 121 (21.49%)
occurrences (all)	39	25	31

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2013	Addition of an inclusion criteria to only include subjects who are at least 18 years of age. Addition of an inclusion criteria for sexually active males and/or their partners to use effective birth control during the treatment period and for 6 months after last dose of radium-223 dichloride. Revised definition of bone progression based on the adapted PCWG2 criteria for consistency across the radium-223 program following comments from the FDA on another related radium-223 study. This change affected the time points of radiological assessments. Clarification of central review of radiological and quantitated bone scan endpoints. Addition of a study specific dose modification to mandate discontinuation of treatment with radium-223 dichloride in subjects who experience Grade 4 neutropenia lasting > 7 days despite adequate treatment.
19 November 2013	Reorganization of the inclusion criterion to specify serum PSA ≥ 2 ng/mL as an inclusion criterion for castration-resistant disease. Update to the radium-223 dichloride dosing and dose calibration to reflect the revised NIST standard. Removal of the dosing restriction with bisphosphonates Addition of an efficacy analysis set (Week 24 analysis set).
13 August 2015	Update to procedures for long-term follow-up. Update to analysis for Comparison 2 from 24 weeks to the 6th dose.
16 May 2017	Addition that radium-223 dichloride should not be given with abiraterone plus prednisone/prednisolone. New request that bone fractures and bone associated events (e.g., osteoporosis) need to be reported as (S)AEs, including during long term follow-up, regardless of causality to study treatment. Based on the available data on radium-223 dichloride, initiation of BHAs during the follow-up periods, including bisphosphonates or denosumab, should be considered, taking into consideration applicable guidelines.

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.

Arms in active follow-up period were mutually exclusive, it was marked no due to database constraints (period start number must equal completed number of preceding period.)

Notes: