Clinical trial results:
A Phase 4 long-term follow-up study to define the safety profile of radium-223 dichloride

Summary

EudraCT number	2014-002407-25
Trial protocol	DE SE ES FR BE CZ GB FI PL
Global end of trial date	31 January 2024

Results information

Result version number	v1 (current)
This version publication date	25 January 2025
First version publication date	25 January 2025

Trial information

Trial identification

Sponsor protocol code	BAY88-8223/16996

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02312960
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, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area, Bayer AG, +49 30 300139003, clinica-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	31 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives are to define the long-term safety profile of radium-223 dichloride (for up to 7 years after the last dose of radium-223 dichloride); to assess the incidence of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy; to assess the incidence of bone fractures and bone associated events (e.g., osteoporosis); and, in subjects who receive cytotoxic chemotherapy, to assess the incidence of febrile neutropenia or hemorrhage during their chemotherapy treatment and for up to 6 months thereafter at a frequency based on local clinical practice.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	85 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Israel: 21

Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 20
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	255
EEA total number of subjects	105

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)	81
From 65 to 84 years	168
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in 22 countries between 18-Dec-2014 (first subject first visit) and 31-Jan-2024 (last subject last visit).

Pre-assignment

Screening details:

A total of 257 participants were screened from the selected feeder studies into the 16996 study for long-term follow-up. Of these, 255 participants entered the study and 2 participants did not complete screening.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Feeder trials subjects enrolled into this long-term safety follow-up study

Arms

Are arms mutually exclusive?	Yes
Arm title	From study 15396 Radium-223 dichloride+Abi/Pred group

Arm description:

Safety follow up from feeder study 15396. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) at intervals of every 4 weeks, along with abiraterone acetate plus prednisone/prednisolone (abi/pred) for up to 6 cycles.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received prednisone/prednisolone in the selected feeder study.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received abiraterone acetate in the selected feeder study.

Arm title	From study 15396 Placebo+Abi/Pred group

Arm description:

Safety follow up from feeder study 15396. Participants received placebo matched to radium-223 dichloride at intervals of every 4 weeks, along with abiraterone acetate plus prednisone/prednisolone (abi/pred) for up to 6 cycles.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received abiraterone acetate in the selected feeder study.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received at least 1 dose of placebo-matched radium-223 dichloride in the selected feeder study.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received prednisone/prednisolone in the selected feeder study.

Arm title	From study 16216 Radium-223 dichloride group

Arm description:

Safety follow up from feeder study 16216. Participants received radium-223 dichloride 50 kBg/kg at intervals of every 4 weeks for up to 6 cycles.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

Arm title	From study 16298 Radium-223 dichloride+hormonal therapy group

Arm description:

Safety follow up from feeder study 16298. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with single hormonal agent, for up to 6 cycles.

Arm type	Experimental

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

Arm title	From study 16298 Placebo + hormonal therapy group

Arm description:

Safety follow up from feeder study 16298. Participants received placebo matched to radium-223 dichloride at intervals of every 4 weeks, along with single hormonal agent for up to 6 cycles.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received at least 1 dose of placebo-matched radium-223 dichloride in the selected feeder study.

Arm title	From study 16506 Radium-223 dichloride group

Arm description:

Safety follow up from feeder study 16506. Participants received radium-223 dichloride 50 kBg/kg at intervals of every 4 weeks for up to 6 cycles.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

Arm title	From study 16507 Radium-223 dichloride treatment A group

Arm description:

Safety follow up from feeder study 16507. Participants received radium-223 dichloride 55 kBg/kg at intervals of every 4 weeks for up to 6 cycles.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

Arm title	From study 16507 Radium-223 dichloride treatment B group

Arm description:

Safety follow up from feeder study 16507. Participants received radium-223 dichloride 88 kBg/kg at intervals of every 4 weeks for up to 6 cycles.

Arm type	Experimental

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

Arm title	From study 16507 Radium-223 dichloride treatment C group

Arm description:

Safety follow up from feeder study 16507. Participants received radium-223 dichloride 55 kBg/kg at intervals of every 4 weeks for up to 12 cycles.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

Arm title	From study 16544 Radium-223 dichloride+Abi/Pred group

Arm description:

Safety follow up from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with Abi/Pred for up to 6 cycles.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received prednisone/prednisolone in the selected feeder study.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received abiraterone acetate in the selected feeder study.

Arm title	From study 16544 Radium-223 dichloride+enzalutamide group

Arm description:

Safety follow up from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with enzalutamide for up to 6 cycles.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received enzalutamide in the selected feeder study.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

Arm title	From study 16544 Radium-223 dichloride group

Arm description:

Safety follow up from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks for up to 6 cycles.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

Arm title	From study 17096 Radium-223 dichloride + EXE/EVE group

Arm description:

Safety follow up from feeder study 17096. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) along with exemestane (EXE) + everolimus (EVE) once daily.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received everolimus in the selected feeder study.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received exemestane in the selected feeder study.

Arm title	From study 17096 Placebo + EXE/EVEgroup

Arm description:

Safety follow up from feeder study 17096. Participants received placebo matched to radium-223 dichloride along with exemestane (EXE) + everolimus (EVE) once daily.

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

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Eligible subjects had received at least 1 dose of radium-223 dichloride in the selected feeder trials.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received exemestane in the selected feeder study.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No study treatment was provided in this long-term follow-up study. Subjects in this group had received everolimus in the selected feeder study.

Number of subjects in period 1	From study 15396 Radium-223 dichloride+Abi/Pred group	From study 15396 Placebo+Abi/Pred group	From study 16216 Radium-223 dichloride group
Started	39	49	31
Completed	14	15	3
Not completed	25	34	28
Consent withdrawn by subject	1	2	-
Death	24	32	25

Lost to follow-up	-	-	1
Missing	-	-	2

Number of subjects in period 1	From study 16298 Radium-223 dichloride+hormonal therapy group	From study 16298 Placebo + hormonal therapy group	From study 16506 Radium-223 dichloride group
Started	14	9	5
Completed	3	3	0
Not completed	11	6	5
Consent withdrawn by subject	-	1	-
Death	11	5	5
Lost to follow-up	-	-	-
Missing	-	-	-

Number of subjects in period 1	From study 16507 Radium-223 dichloride treatment A group	From study 16507 Radium-223 dichloride treatment B group	From study 16507 Radium-223 dichloride treatment C group
Started	11	9	11
Completed	1	1	2
Not completed	10	8	9
Consent withdrawn by subject	1	2	2
Death	8	5	7
Lost to follow-up	1	1	-
Missing	-	-	-

Number of subjects in period 1	From study 16544 Radium-223 dichloride+Abi/Pred group	From study 16544 Radium-223 dichloride+enzalutamide group	From study 16544 Radium-223 dichloride group
Started	9	4	3
Completed	2	1	2
Not completed	7	3	1
Consent withdrawn by subject	3	-	-
Death	3	3	1
Lost to follow-up	1	-	-
Missing	-	-	-

Number of subjects in period 1	From study 17096 Radium-223 dichloride + EXE/EVE group	From study 17096 Placebo + EXE/EVEgroup
Started	33	28
Completed	5	9
Not completed	28	19
Consent withdrawn by subject	2	-
Death	25	19
Lost to follow-up	1	-
Missing	-	-

Reporting groups

Reporting group title	From study 15396 Radium-223 dichloride+Abi/Pred group
Reporting group description:	
Safety follow up from feeder study 15396. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) at intervals of every 4 weeks, along with abiraterone acetate plus prednisone/prednisolone (abi/pred) for up to 6 cycles.	
Reporting group title	From study 15396 Placebo+Abi/Pred group
Reporting group description:	
Safety follow up from feeder study 15396. Participants received placebo matched to radium-223 dichloride at intervals of every 4 weeks, along with abiraterone acetate plus prednisone/prednisolone (abi/pred) for up to 6 cycles.	
Reporting group title	From study 16216 Radium-223 dichloride group
Reporting group description:	
Safety follow up from feeder study 16216. Participants received radium-223 dichloride 50 kBg/kg at intervals of every 4 weeks for up to 6 cycles.	
Reporting group title	From study 16298 Radium-223 dichloride+hormonal therapy group
Reporting group description:	
Safety follow up from feeder study 16298. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with single hormonal agent, for up to 6 cycles.	
Reporting group title	From study 16298 Placebo + hormonal therapy group
Reporting group description:	
Safety follow up from feeder study 16298. Participants received placebo matched to radium-223 dichloride at intervals of every 4 weeks, along with single hormonal agent for up to 6 cycles.	
Reporting group title	From study 16506 Radium-223 dichloride group
Reporting group description:	
Safety follow up from feeder study 16506. Participants received radium-223 dichloride 50 kBg/kg at intervals of every 4 weeks for up to 6 cycles.	
Reporting group title	From study 16507 Radium-223 dichloride treatment A group
Reporting group description:	
Safety follow up from feeder study 16507. Participants received radium-223 dichloride 55 kBg/kg at intervals of every 4 weeks for up to 6 cycles.	
Reporting group title	From study 16507 Radium-223 dichloride treatment B group
Reporting group description:	
Safety follow up from feeder study 16507. Participants received radium-223 dichloride 88 kBg/kg at intervals of every 4 weeks for up to 6 cycles.	
Reporting group title	From study 16507 Radium-223 dichloride treatment C group
Reporting group description:	
Safety follow up from feeder study 16507. Participants received radium-223 dichloride 55 kBg/kg at intervals of every 4 weeks for up to 12 cycles.	
Reporting group title	From study 16544 Radium-223 dichloride+Abi/Pred group
Reporting group description:	
Safety follow up from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with Abi/Pred for up to 6 cycles.	
Reporting group title	From study 16544 Radium-223 dichloride+enzalutamide group
Reporting group description:	
Safety follow up from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with enzalutamide for up to 6 cycles.	
Reporting group title	From study 16544 Radium-223 dichloride group

Reporting group description:

Safety follow up from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks for up to 6 cycles.

Reporting group title	From study 17096 Radium-223 dichloride + EXE/EVE group

Reporting group description:

Safety follow up from feeder study 17096. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) along with exemestane (EXE) + everolimus (EVE) once daily.

Reporting group title	From study 17096 Placebo + EXE/EVEgroup

Reporting group description:

Safety follow up from feeder study 17096. Participants received placebo matched to radium-223 dichloride along with exemestane (EXE) + everolimus (EVE) once daily.

Reporting group values	From study 15396 Radium-223 dichloride+Abi/Pred group	From study 15396 Placebo+Abi/Pred group	From study 16216 Radium-223 dichloride group
Number of subjects	39	49	31
Age Categorical Units: Subjects			
Adults (18-64 years)	6	3	3
From 65-84 years	32	44	28
85 years and over	1	2	0
Age Continuous Units: years			
median	73.0	75.0	73.0
full range (min-max)	51 to 86	60 to 92	59 to 80
Gender Categorical Units: Subjects			
Female	0	0	0
Male	39	49	31
Race Units: Subjects			
White	29	30	31
Black or African American	1	0	0
Asian	6	13	0
Not reported	2	4	0
Missing	1	2	0
Ethnicity Units: Subjects			
Hispanic or Latino	4	4	0
Not Hispanic or Latino	32	41	31
Not reported	3	4	0

Reporting group values	From study 16298 Radium-223 dichloride+hormonal therapy group	From study 16298 Placebo + hormonal therapy group	From study 16506 Radium-223 dichloride group
Number of subjects	14	9	5
Age Categorical Units: Subjects			
Adults (18-64 years)	9	5	2
From 65-84 years	5	4	3

85 years and over	0	0	0

Age Continuous Units: years			
median	57.5	57.0	66.0
full range (min-max)	29 to 83	42 to 79	55 to 79
Gender Categorical Units: Subjects			
Female	14	9	0
Male	0	0	5
Race Units: Subjects			
White	9	7	5
Black or African American	0	0	0
Asian	4	2	0
Not reported	1	0	0
Missing	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	13	9	5
Not reported	1	0	0

Reporting group values	From study 16507 Radium-223 dichloride treatment A group	From study 16507 Radium-223 dichloride treatment B group	From study 16507 Radium-223 dichloride treatment C group
Number of subjects	11	9	11
Age Categorical Units: Subjects			
Adults (18-64 years)	1	2	5
From 65-84 years	9	7	6
85 years and over	1	0	0
Age Continuous Units: years			
median	75.0	69.0	65.0
full range (min-max)	63 to 87	63 to 84	55 to 82
Gender Categorical Units: Subjects			
Female	0	0	0
Male	11	9	11
Race Units: Subjects			
White	7	4	7
Black or African American	0	0	1
Asian	4	5	2
Not reported	0	0	1
Missing	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	1

Not Hispanic or Latino	11	9	10
Not reported	0	0	0

Reporting group values	From study 16544 Radium-223 dichloride+Abi/Pred group	From study 16544 Radium-223 dichloride+enzalutamide group	From study 16544 Radium-223 dichloride group
Number of subjects	9	4	3
Age Categorical Units: Subjects			
Adults (18-64 years)	1	1	1
From 65-84 years	7	3	2
85 years and over	1	0	0
Age Continuous Units: years			
median	72.0	75.0	68.0
full range (min-max)	60 to 88	61 to 78	62 to 75
Gender Categorical Units: Subjects			
Female	0	0	0
Male	9	4	3
Race Units: Subjects			
White	7	3	3
Black or African American	2	0	0
Asian	0	0	0
Not reported	0	1	0
Missing	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	8	3	3
Not reported	0	0	0

Reporting group values	From study 17096 Radium-223 dichloride + EXE/EVE group	From study 17096 Placebo + EXE/EVEgroup	Total
Number of subjects	33	28	255
Age Categorical Units: Subjects			
Adults (18-64 years)	26	16	81
From 65-84 years	6	12	168
85 years and over	1	0	6
Age Continuous Units: years			
median	59.0	59.0	
full range (min-max)	42 to 88	43 to 78	-
Gender Categorical Units: Subjects			
Female	33	28	84
Male	0	0	171

Race Units: Subjects			
White	21	20	183
Black or African American	0	0	4
Asian	10	7	53
Not reported	2	1	12
Missing	0	0	3
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	13
Not Hispanic or Latino	30	27	232
Not reported	2	0	10

Subject analysis sets

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

Subject analysis set description:

All subjects received at least 1 dose of radium-223 dichloride or placebo in the feeder studies.

Reporting group values	Safety analysis set (SAF)		
Number of subjects	255		
Age Categorical Units: Subjects			
Adults (18-64 years)	81		
From 65-84 years	168		
85 years and over	6		
Age Continuous Units: years median full range (min-max)			
Gender Categorical Units: Subjects			
Female Male			
Race Units: Subjects			
White Black or African American Asian Not reported Missing			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Not reported			

End points

End points reporting groups

Reporting group title	From study 15396 Radium-223 dichloride+Abi/Pred group
Reporting group description:	
Safety follow up from feeder study 15396. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) at intervals of every 4 weeks, along with abiraterone acetate plus prednisone/prednisolone (abi/pred) for up to 6 cycles.	
Reporting group title	From study 15396 Placebo+Abi/Pred group
Reporting group description:	
Safety follow up from feeder study 15396. Participants received placebo matched to radium-223 dichloride at intervals of every 4 weeks, along with abiraterone acetate plus prednisone/prednisolone (abi/pred) for up to 6 cycles.	
Reporting group title	From study 16216 Radium-223 dichloride group
Reporting group description:	
Safety follow up from feeder study 16216. Participants received radium-223 dichloride 50 kBg/kg at intervals of every 4 weeks for up to 6 cycles.	
Reporting group title	From study 16298 Radium-223 dichloride+hormonal therapy group
Reporting group description:	
Safety follow up from feeder study 16298. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with single hormonal agent, for up to 6 cycles.	
Reporting group title	From study 16298 Placebo + hormonal therapy group
Reporting group description:	
Safety follow up from feeder study 16298. Participants received placebo matched to radium-223 dichloride at intervals of every 4 weeks, along with single hormonal agent for up to 6 cycles.	
Reporting group title	From study 16506 Radium-223 dichloride group
Reporting group description:	
Safety follow up from feeder study 16506. Participants received radium-223 dichloride 50 kBg/kg at intervals of every 4 weeks for up to 6 cycles.	
Reporting group title	From study 16507 Radium-223 dichloride treatment A group
Reporting group description:	
Safety follow up from feeder study 16507. Participants received radium-223 dichloride 55 kBg/kg at intervals of every 4 weeks for up to 6 cycles.	
Reporting group title	From study 16507 Radium-223 dichloride treatment B group
Reporting group description:	
Safety follow up from feeder study 16507. Participants received radium-223 dichloride 88 kBg/kg at intervals of every 4 weeks for up to 6 cycles.	
Reporting group title	From study 16507 Radium-223 dichloride treatment C group
Reporting group description:	
Safety follow up from feeder study 16507. Participants received radium-223 dichloride 55 kBg/kg at intervals of every 4 weeks for up to 12 cycles.	
Reporting group title	From study 16544 Radium-223 dichloride+Abi/Pred group
Reporting group description:	
Safety follow up from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with Abi/Pred for up to 6 cycles.	
Reporting group title	From study 16544 Radium-223 dichloride+enzalutamide group
Reporting group description:	
Safety follow up from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with enzalutamide for up to 6 cycles.	
Reporting group title	From study 16544 Radium-223 dichloride group

Reporting group description:

Safety follow up from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks for up to 6 cycles.

Reporting group title	From study 17096 Radium-223 dichloride + EXE/EVE group

Reporting group description:

Safety follow up from feeder study 17096. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) along with exemestane (EXE) + everolimus (EVE) once daily.

Reporting group title	From study 17096 Placebo + EXE/EVEgroup

Reporting group description:

Safety follow up from feeder study 17096. Participants received placebo matched to radium-223 dichloride along with exemestane (EXE) + everolimus (EVE) once daily.

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

Subject analysis set description:

All subjects received at least 1 dose of radium-223 dichloride or placebo in the feeder studies.

Primary: Number of subjects and severity of radium-223 dichloride-/placebo-related Adverse Events (AEs)

End point title	Number of subjects and severity of radium-223 dichloride-/placebo-related Adverse Events (AEs)[1]

End point description:

End point type	Primary

End point timeframe:

Up to 7 years after the last dose of radium-223 dichloride or placebo in the feeder studies.

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 incidence of serious and high-grade long-term AEs was too limited to support statistical analysis. Accordingly, only descriptive summaries are included in the results.

End point values	From study 15396 Radium-223 dichloride+Abi/Pred group	From study 15396 Placebo+Abi/Pred group	From study 16216 Radium-223 dichloride group	From study 16298 Radium-223 dichloride+hormonal therapy group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	49	31	14
Units: Subjects				
Radium-223/Placebo-related AE	0	1	1	0
Grade 1	0	1	0	0
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	1	0
Grade 5	0	0	0	0

End point values	From study 16298 Placebo + hormonal therapy group	From study 16506 Radium-223 dichloride group	From study 16507 Radium-223 dichloride treatment A group	From study 16507 Radium-223 dichloride treatment B group

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	5	11	9
Units: Subjects				
Radium-223/Placebo-related AE	0	0	1	0
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	1	0

End point values	From study 16507 Radium-223 dichloride treatment C group	From study 16544 Radium-223 dichloride+Abi/Pred group	From study 16544 Radium-223 dichloride+enzalutamide group	From study 16544 Radium-223 dichloride group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	4	3
Units: Subjects				
Radium-223/Placebo-related AE	3	0	0	1
Grade 1	0	0	0	0
Grade 2	2	0	0	0
Grade 3	1	0	0	1
Grade 4	0	0	0	0
Grade 5	0	0	0	0

End point values	From study 17096 Radium-223 dichloride + EXE/EVE group	From study 17096 Placebo + EXE/EVEgroup	Safety analysis set (SAF)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	28	255	
Units: Subjects				
Radium-223/Placebo-related AE	3	0	10	
Grade 1	0	0	1	
Grade 2	1	0	3	
Grade 3	2	0	4	
Grade 4	0	0	1	
Grade 5	0	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with radium-223 dichloride-/placebo-related Serious Adverse Events (SAEs)

End point title	Number of subjects with radium-223 dichloride-/placebo-related Serious Adverse Events (SAEs)[2]

End point description:

End point type	Primary

End point timeframe:

Up to 7 years after the last dose of radium-223 dichloride or placebo in the feeder studies.

Notes:

[2] - 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 incidence of serious and high-grade long-term AEs was too limited to support statistical analysis. Accordingly, only descriptive summaries are included in the results.

End point values	From study 15396 Radium-223 dichloride+Abi/Pred group	From study 15396 Placebo+Abi/Pred group	From study 16216 Radium-223 dichloride group	From study 16298 Radium-223 dichloride+hormonal therapy group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	49	31	14
Units: Subjects				
Radium-223/Placebo-related SAE	0	0	1	0

End point values	From study 16298 Placebo + hormonal therapy group	From study 16506 Radium-223 dichloride group	From study 16507 Radium-223 dichloride treatment A group	From study 16507 Radium-223 dichloride treatment B group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	5	11	9
Units: Subjects				
Radium-223/Placebo-related SAE	0	0	1	0

End point values	From study 16507 Radium-223 dichloride treatment C group	From study 16544 Radium-223 dichloride+Abi/Pred group	From study 16544 Radium-223 dichloride+enzalutamide group	From study 16544 Radium-223 dichloride group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	4	3
Units: Subjects				
Radium-223/Placebo-related SAE	2	0	0	0

End point values	From study 17096 Radium-223 dichloride + EXE/EVE group	From study 17096 Placebo + EXE/EVEgroup	Safety analysis set (SAF)	

Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	28	255	
Units: Subjects				
Radium-223/Placebo-related SAE	1	0	5	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy

End point title	Number of subjects with leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy[3]

End point description:

End point type	Primary

End point timeframe:

Up to 7 years after the last dose of radium-223 dichloride or placebo in the feeder studies.

Notes:

[3] - 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 incidence of serious and high-grade long-term AEs was too limited to support statistical analysis. Accordingly, only descriptive summaries are included in the results.

End point values	From study 15396 Radium-223 dichloride+Abi/Pred group	From study 15396 Placebo+Abi/Pred group	From study 16216 Radium-223 dichloride group	From study 16298 Radium-223 dichloride+hormonal therapy group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	49	31	14
Units: Subjects				
Leukemia	0	0	1	0
Myelodysplastic syndrome	0	0	0	0
Aplastic anemia	0	0	0	0
Primary bone cancer	0	0	0	0
Any other new primary malignancy	1	1	1	0

End point values	From study 16298 Placebo + hormonal therapy group	From study 16506 Radium-223 dichloride group	From study 16507 Radium-223 dichloride treatment A group	From study 16507 Radium-223 dichloride treatment B group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	5	11	9
Units: Subjects				
Leukemia	0	0	1	0
Myelodysplastic syndrome	0	0	0	0
Aplastic anemia	0	0	0	0

Primary bone cancer	0	0	0	0
Any other new primary malignancy	0	0	0	1

End point values	From study 16507 Radium-223 dichloride treatment C group	From study 16544 Radium-223 dichloride+Abi/Pred group	From study 16544 Radium-223 dichloride+enzalutamide group	From study 16544 Radium-223 dichloride group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	4	3
Units: Subjects				
Leukemia	0	0	0	0
Myelodysplastic syndrome	0	0	0	0
Aplastic anemia	0	0	0	0
Primary bone cancer	0	0	0	0
Any other new primary malignancy	0	0	0	0

End point values	From study 17096 Radium-223 dichloride + EXE/EVE group	From study 17096 Placebo + EXE/EVEgroup	Safety analysis set (SAF)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	28	255	
Units: Subjects				
Leukemia	0	0	2	
Myelodysplastic syndrome	0	0	0	
Aplastic anemia	1	0	1	
Primary bone cancer	0	0	0	
Any other new primary malignancy	0	0	4	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with bone fractures and bone associated events

End point title	Number of subjects with bone fractures and bone associated events[4]

End point description:

Bone fractures and Bone associated events (e.g., osteoporosis), regardless of investigator assessment of causality.

End point type	Primary

End point timeframe:

Up to 7 years after the last dose of radium-223 dichloride or placebo in the feeder studies.

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 incidence of serious and high-grade long-term AEs was too limited to support statistical analysis. Accordingly, only descriptive summaries are included in the results.

End point values	From study 15396 Radium-223 dichloride+Abi/Pred group	From study 15396 Placebo+Abi/Pred group	From study 16216 Radium-223 dichloride group	From study 16298 Radium-223 dichloride+hormonal therapy group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	49	31	14
Units: Subjects				
Bone fractures	3	6	1	1
Bone associated events	1	2	1	2

End point values	From study 16298 Placebo + hormonal therapy group	From study 16506 Radium-223 dichloride group	From study 16507 Radium-223 dichloride treatment A group	From study 16507 Radium-223 dichloride treatment B group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	5	11	9
Units: Subjects				
Bone fractures	3	0	1	2
Bone associated events	0	0	0	1

End point values	From study 16507 Radium-223 dichloride treatment C group	From study 16544 Radium-223 dichloride+Abi/Pred group	From study 16544 Radium-223 dichloride+enzalutamide group	From study 16544 Radium-223 dichloride group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	4	3
Units: Subjects				
Bone fractures	3	1	2	0
Bone associated events	4	2	0	1

End point values	From study 17096 Radium-223 dichloride + EXE/EVE group	From study 17096 Placebo + EXE/EVEgroup	Safety analysis set (SAF)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	28	255	
Units: Subjects				
Bone fractures	6	7	36	

Bone associated events	3	0	17	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with febrile neutropenia or hemorrhage

End point title	Number of subjects with febrile neutropenia or hemorrhage[5]

End point description:

Only for subjects who received cytotoxic chemotherapy in feeder studies.

End point type	Primary

End point timeframe:

During chemotherapy treatment and for up to 6 months thereafter

Notes:

[5] - 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 incidence of serious and high-grade long-term AEs was too limited to support statistical analysis. Accordingly, only descriptive summaries are included in the results.

End point values	From study 15396 Radium-223 dichloride+Abi/Pred group	From study 15396 Placebo+Abi/Pred group	From study 16216 Radium-223 dichloride group	From study 16298 Radium-223 dichloride+hormonal therapy group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	49	31	14
Units: Subjects				
Febrile neutropenia	0	0	0	1
Hemorrhage	0	0	0	0

End point values	From study 16298 Placebo + hormonal therapy group	From study 16506 Radium-223 dichloride group	From study 16507 Radium-223 dichloride treatment A group	From study 16507 Radium-223 dichloride treatment B group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	5	11	9
Units: Subjects				
Febrile neutropenia	0	0	1	1
Hemorrhage	0	0	0	0

End point values	From study 16507 Radium-223 dichloride treatment C	From study 16544 Radium-223 dichloride+Abi/	From study 16544 Radium-223 dichloride+enz	From study 16544 Radium-223 dichloride group

	group	Pred group	alutamide group	
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	4	3
Units: Subjects				
Febrile neutropenia	0	0	0	0
Hemorrhage	0	0	0	0

End point values	From study 17096 Radium-223 dichloride + EXE/EVE group	From study 17096 Placebo + EXE/EVEgroup	Safety analysis set (SAF)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	28	255	
Units: Subjects				
Febrile neutropenia	1	0	4	
Hemorrhage	0	2	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 7 years

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	From study 15396 Radium-223 dichloride+Abi/Pred group

Reporting group description:

Safety FU from feeder study 15396. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) at intervals of every 4 weeks, along with abiraterone acetate plus prednisone/prednisolone (abi/pred) for up to 6 cycles.

Reporting group title	From study 16216 Radium-223 dichloride group

Reporting group description:

Safety FU from feeder study 16216. Participants received radium-223 dichloride 50 kBg/kg at intervals of every 4 weeks for up to 6 cycles.

Reporting group title	From study 16298 Radium-223 dichloride+hormonal therapy group

Reporting group description:

Safety FU from feeder study 16298. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with single hormonal agent, for up to 6 cycles.

Reporting group title	From study 16298 Placebo + hormonal therapy group

Reporting group description:

Safety FU from feeder study 16298. Participants received placebo matched to radium-223 dichloride at intervals of every 4 weeks, along with single hormonal agent for up to 6 cycles.

Reporting group title	From study 16506 Radium-223 dichloride group

Reporting group description:

Safety FU from feeder study 16506. Participants received radium-223 dichloride 50 kBg/kg at intervals of every 4 weeks for up to 6 cycles.

Reporting group title	From study 17096 Placebo + EXE/EVEgroup

Reporting group description:

Safety FU from feeder study 17096. Participants received placebo matched to radium-223 dichloride along with exemestane (EXE) + everolimus (EVE) once daily.

Reporting group title	From study 16507 Radium-223 dichloride treatment B group

Reporting group description:

Safety FU from feeder study 16507. Participants received radium-223 dichloride 88 kBg/kg at intervals of every 4 weeks for up to 6 cycles.

Reporting group title	From study 16507 Radium-223 dichloride treatment C group

Reporting group description:

Safety FU from feeder study 16507. Participants received radium-223 dichloride 55 kBg/kg at intervals of every 4 weeks for up to 12 cycles.

Reporting group title	From study 16544 Radium-223 dichloride+Abi/Pred group

Reporting group description:

Safety FU from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with Abi/Pred for up to 6 cycles.

Reporting group title	From study 16544 Radium-223 dichloride+enzalutamide group

Reporting group description:

Safety FU from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks, along with enzalutamide for up to 6

cycles.

Reporting group title	From study 16544 Radium-223 dichloride group
Reporting group description:	
Safety FU from feeder study 16544. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) at intervals of every 4 weeks for up to 6 cycles.	
Reporting group title	From study 17096 Radium-223 dichloride + EXE/EVE group
Reporting group description:	
Safety FU from feeder study 17096. Participants received radium-223 dichloride 50 kBg/kg (55 kBq/kg after implementation of NIST update) along with exemestane (EXE) + everolimus (EVE) once daily.	
Reporting group title	From study 15396 Placebo+Abi/Pred group
Reporting group description:	
Safety FU from feeder study 15396. Participants received placebo matched to radium-223 dichloride at intervals of every 4 weeks, along with abiraterone acetate plus prednisone/prednisolone (abi/pred) for up to 6 cycles.	
Reporting group title	From study 16507 Radium-223 dichloride treatment A group
Reporting group description:	
Safety FU from feeder study 16507. Participants received radium-223 dichloride 55 kBg/kg at intervals of every 4 weeks for up to 6 cycles.	

Serious adverse events	From study 15396 Radium-223 dichloride+Abi/Pred group	From study 16216 Radium-223 dichloride group	From study 16298 Radium-223 dichloride+hormonal therapy group
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 39 (7.69%)	4 / 31 (12.90%)	1 / 14 (7.14%)
number of deaths (all causes)	24	25	11
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 31 (3.23%)	0 / 14 (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
Cholangiocarcinoma			
subjects affected / exposed	0 / 39 (0.00%)	1 / 31 (3.23%)	0 / 14 (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
Colon cancer metastatic			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			

subjects affected / exposed	1 / 39 (2.56%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 39 (0.00%)	1 / 31 (3.23%)	0 / 14 (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
Foot fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Spinal cord compression			
subjects affected / exposed	1 / 39 (2.56%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Aplastic anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoporotic fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 39 (2.56%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 39 (0.00%)	1 / 31 (3.23%)	0 / 14 (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

Serious adverse events	From study 16298 Placebo + hormonal therapy group	From study 16506 Radium-223 dichloride group	From study 17096 Placebo + EXE/EVEgroup
Total subjects affected by serious			

adverse events			
subjects affected / exposed	1 / 9 (11.11%)	0 / 5 (0.00%)	6 / 28 (21.43%)
number of deaths (all causes)	5	5	19
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer metastatic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Foot fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aplastic anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoporotic fracture			

subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 5 (0.00%)	3 / 28 (10.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	From study 16507 Radium-223 dichloride treatment B group	From study 16507 Radium-223 dichloride treatment C group	From study 16544 Radium-223 dichloride+Abi/Pred group
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	3 / 11 (27.27%)	0 / 9 (0.00%)
number of deaths (all causes)	5	7	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer metastatic			

subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 9 (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
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			

subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 9 (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
Aplastic anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoporotic fracture			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 9 (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
Spondylolisthesis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 9 (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 / 9 (0.00%)	1 / 11 (9.09%)	0 / 9 (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

Serious adverse events	From study 16544 Radium-223 dichloride+enzalutamide group	From study 16544 Radium-223 dichloride group	From study 17096 Radium-223 dichloride + EXE/EVE group
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	4 / 33 (12.12%)
number of deaths (all causes)	3	1	25
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer metastatic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 33 (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
Ankle fracture			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aplastic anaemia			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 33 (3.03%)
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 and connective tissue disorders			
Osteoporotic fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	From study 15396 Placebo+Abi/Pred group	From study 16507 Radium-223 dichloride treatment A group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 49 (8.16%)	2 / 11 (18.18%)	
number of deaths (all causes)	32	8	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cholangiocarcinoma			

subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoporotic fracture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	2 / 49 (4.08%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			

subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	From study 15396 Radium-223 dichloride+Abi/Pred group	From study 16216 Radium-223 dichloride group	From study 16298 Radium-223 dichloride+hormonal therapy group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 39 (5.13%)	0 / 31 (0.00%)	3 / 14 (21.43%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	1 / 39 (2.56%)	0 / 31 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Radius fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Craniofacial fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Spinal compression fracture			

subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rib fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Genital haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Osteoporosis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Osteoarthritis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Osteoporotic fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pathological fracture			

subjects affected / exposed	1 / 39 (2.56%)	0 / 31 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Osteopenia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Spondylitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Spondylolisthesis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Spinal stenosis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Infections and infestations			
Osteomyelitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Product issues			
Device failure			
subjects affected / exposed	0 / 39 (0.00%)	0 / 31 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	From study 16298 Placebo + hormonal therapy group	From study 16506 Radium-223 dichloride group	From study 17096 Placebo + EXE/EVEgroup
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	0 / 5 (0.00%)	3 / 28 (10.71%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Craniofacial fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Spinal compression fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Rib fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Genital haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Petechiae			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Osteoporosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Osteoporotic fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Pathological fracture			
subjects affected / exposed	3 / 9 (33.33%)	0 / 5 (0.00%)	1 / 28 (3.57%)
occurrences (all)	3	0	2
Osteopenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Spondylitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Spondylolisthesis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Spinal stenosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Osteomyelitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Product issues			

Device failure			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	From study 16507 Radium-223 dichloride treatment B group	From study 16507 Radium-223 dichloride treatment C group	From study 16544 Radium-223 dichloride+Abi/Pred group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	3 / 11 (27.27%)	3 / 9 (33.33%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Craniofacial fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Spinal compression fracture			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Rib fracture			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Genital haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Osteoporosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Osteoporotic fracture			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pathological fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Osteopenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Spondylitis			

subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Spondylolisthesis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 11 (18.18%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Spinal stenosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Osteomyelitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Product issues			
Device failure			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	From study 16544 Radium-223 dichloride+enzalutamide group	From study 16544 Radium-223 dichloride group	From study 17096 Radium-223 dichloride + EXE/EVE group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	8 / 33 (24.24%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Foot fracture			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Craniofacial fracture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Spinal compression fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Rib fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Eye disorders			
Cataract			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Genital haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Osteoporosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Osteoporotic fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Pathological fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	5 / 33 (15.15%)
occurrences (all)	0	0	10
Osteopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Spondylitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Spondylolisthesis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Spinal stenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	3 / 33 (9.09%)
occurrences (all)	0	0	3
Infections and infestations			
Osteomyelitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Product issues			
Device failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	From study 15396	From study 16507	

	Placebo+Abi/Pred group	Radium-223 dichloride treatment A group	
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 49 (12.24%)	1 / 11 (9.09%)	
Investigations Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Injury, poisoning and procedural complications Ankle fracture subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 11 (0.00%) 0	
Foot fracture subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Radius fracture subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Craniofacial fracture subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Spinal compression fracture subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Rib fracture subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Eye disorders Cataract			

subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Genital haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Osteoporosis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Osteoarthritis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Osteoporotic fracture			
subjects affected / exposed	1 / 49 (2.04%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Pathological fracture			
subjects affected / exposed	3 / 49 (6.12%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Osteopenia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Spondylitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Spondylolisthesis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	

Spinal stenosis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Osteonecrosis of jaw subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 11 (0.00%) 0	
Infections and infestations Osteomyelitis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	
Product issues Device failure subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 11 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2016	Global amendment 01 forming integrated protocol Version 2.0 introduced the following changes: Clarified that all cytotoxic chemotherapy and radiotherapy received by participants was to be recorded for this study; removed overall survival as secondary objective and removed reference to an interim analysis; clarified the selected safety variables collected in the 16996 study and detailed the plan for pooling and presenting feeder study data. Added an option for the study site to obtain information directly from the participant's primary health care professional or caregiver. Removed references to collection of medical history.
11 April 2018	Global amendment 02 forming integrated protocol Version 3.0 introduced the following changes: Updated indications to include breast cancer and multiple myeloma. Added 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 investigator's causality assessment. Added that radium-223 dichloride should not be given with abiraterone plus prednisone/prednisolone. Added statement that initiation of a bone health agent (BHA), including bisphosphonates or denosumab, should be considered taking into consideration applicable guidelines. Any BHA treatment taken during the study period must be recorded. Clarified that participants are permitted to take concomitant medications as part of a clinical trial while participating in the current study. Clarified reporting of related SAEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported