Clinical trial results:
REASURE: A phase II randomised trial of biomarkers to assess (dose-) response in patients with metastatic castration resistant prostate cancer treated with radium-223

Summary

EudraCT number	2013-004055-20
Trial protocol	GB
Global end of trial date	06 October 2023

Results information

Result version number	v1 (current)
This version publication date	17 October 2024
First version publication date	17 October 2024
Summary attachment (see zip file)	Radium-223 in metastatic castration-resistant prostate cancer: whole-body diffusion-weighted magnetic resonance imaging scanning to assess response (Published version - Parker et al.pdf)

Trial information

Trial identification

Sponsor protocol code	CCR4108

Additional study identifiers

ISRCTN number	ISRCTN17805587
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC Reference Number: 14/LO/1385, ICR-CTSU Protocol Number: ICR-CTSU/2013/10040

Notes:

Sponsors

Sponsor organisation name	Institute of Cancer research
Sponsor organisation address	15 Cotswold Road Sutton, SM2 5NG, London, United Kingdom, SM2 5NG
Public contact	Aude Espinasse, The Institute of Cancer Research, reasure-icrctsu@icr.ac.uk
Scientific contact	Aude Espinasse, The Institute of Cancer Research, REASURE-icrctsu@icr.ac.uk

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	11 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2021
Global end of trial reached?	Yes
Global end of trial date	06 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question is: can response to radium-223, in patients with CRPC and bone metastases, be measured reliably by functional imaging and/or circulating biomarkers? The primary objective is to evaluate patients' response to treatment using a type of imaging technique called whole body diffusion-weighted MRI (DW-MRI).

Protection of trial subjects:

For trial entry and optional tissue donation, patients were given a verbal explanation, discussion and written information. The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patient. Eligible patients were given as much time as they needed to consider, ask questions and come to a decision about entering the trial, prior to giving consent for entering the trial. The patient information sheet described which parties would have access to their identifiable personal information and patients were asked to give consent to this. The trial was overseen by an Independent Data Monitoring Committee, who reviewed the accumulating trial data and could recommend stopping the trial if there was any cause for concern about patient safety and if this were the case the patient's oncologist would be notified.

Background therapy:

none

Evidence for comparator:

The evaluation of bone predominant disease in patients with metastatic prostate cancer remains challenging. As yet, there is no reliable method to assess and quantify treatment response. Therefore bone metastases are often regarded as non-measurable disease by standard RECIST (v1.1)/PCWG2 criteria [40]. Criteria exist which use radiographic changes to measure response but these are relatively insensitive, taking a number of months for changes to occur [41]. In addition, the criterion of sclerosis of previously osteolytic metastases is not relevant for metastatic disease that is predominantly sclerotic at baseline (as is common in prostate cancer). Given that assessment of response of bone metastases is insensitive and often non-specific, in practice a combination of clinical, biochemical (e.g PSA and ALP) and radiological measures are currently used. However, more accurate means of monitoring response are required to inform early treatment failure or success.

Radium-223 was the first bone targeted alpha emitter to be tested in phase III studies. It has demonstrated improved survival for this group of patients with a favourable risk/benefit profile. Radium-223 was approved by the FDA in May 2013 for the treatment of CRPC with bone metastases and was granted marketing authorisation in the EU in November 2013. It is currently authorised to be marketed in more than 43 countries. The present study will explore the role of functional imaging and circulating biomarkers to assess response to radium-223 and potential dose-response relationships.

Actual start date of recruitment	27 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 39
Worldwide total number of subjects	39
EEA total number of subjects	0

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)	2
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 7/2015 and 6/2017, 39 patients were recruited from 3 UK hospital sites.

Pre-assignment

Screening details:

Inclusion criteria included histologically/cytologically confirmed adenocarcinoma of the prostate with castrate resistant disease, serum PSA≥2ng/ml, ECOG performance status 0-2, life expectancy > 6 months, and multiple skeletal metastases (≥2 hotspots).

Period 1

Period 1 title	REASURE trial overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	55 kBq/kg Radium 223

Arm description:

Participants in this arm were allocated to receive 55 kBq/kg of Radium 223. Allocation ratio between the 2 arms was 1:1. Treatment allocation was via minimisation with a random element; balancing factors included patient weight, total ALP and current bisphosphonate use. Dose allocation was not blinded. Patients received treatment with radium-223 at the allocated dose via IV administration every 4 weeks for up to 6 cycles.

Arm type	Experimental
Investigational medicinal product name	Radium 223
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients received treatment with radium-223 at 55 kBq/kg via IV administration every 4 weeks for up to 6 cycles.

Arm title	88 kBq/kg Radium 223

Arm description:

Patients received treatment with radium-223 at the 88 kBq/kg via IV administration every 4 weeks for up to 6 cycles.

Arm type	Experimental
Investigational medicinal product name	Radium 223
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients received treatment with radium-223 at 88 kBq/kg via IV administration every 4 weeks for up to 6 cycles.

Number of subjects in period 1	55 kBq/kg Radium 223	88 kBq/kg Radium 223
Started	20	19
Completed	20	17
Not completed	0	2
Consent withdrawn by subject	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	55 kBq/kg Radium 223
Reporting group description:	
Participants in this arm were allocated to receive 55 kBq/kg of Radium 223. Allocation ratio between the 2 arms was 1:1. Treatment allocation was via minimisation with a random element; balancing factors included patient weight, total ALP and current bisphosphonate use. Dose allocation was not blinded. Patients received treatment with radium-223 at the allocated dose via IV administration every 4 weeks for up to 6 cycles.	
Reporting group title	88 kBq/kg Radium 223
Reporting group description:	
Patients received treatment with radium-223 at the 88 kBq/kg via IV administration every 4 weeks for up to 6 cycles.	

Reporting group values	55 kBq/kg Radium 223	88 kBq/kg Radium 223	Total
Number of subjects	20	19	39
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	1	2
From 65-84 years	19	18	37
85 years and over	0	0	0
Age continuous Units: years			
median	74.9	74.5	
inter-quartile range (Q1-Q3)	72.6 to 80.1	67.4 to 78.1	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	20	19	39
Weight at trial entry Units: Subjects			
<80kg	9	10	19
>=80kg	11	9	20
ALP at trial entry Units: Subjects			
<220 U/L	14	16	30
>=220 U/L	6	3	9
Prior bisphosphonate use Units: Subjects			
Yes	3	2	5
No	17	17	34

EOD grade at trial entry Units: Subjects			
EOD1	10	8	18
EOD2	5	9	14
EOD3	3	1	4
EOD4	2	1	3
Lymh node metastases at diagnosis Units: Subjects			
Yes	1	7	8
No	19	12	31
Gleason score at diagnosis (total) Units: Subjects			
Gleason 6	1	2	3
Gleason 7	7	2	9
Gleason 8	4	5	9
Gleason 9	8	9	17
Missing	0	1	1
Time since histological confirmation of disease to trial entry Units: Years			
median	2.9	3.9	
inter-quartile range (Q1-Q3)	1.7 to 5.6	3.0 to 7.1	-
Time since confirmation of bone metastases to trial entry Units: Years			
median	2.0	2.5	
inter-quartile range (Q1-Q3)	1.2 to 3.9	0.5 to 3.9	-
Time since castration resistance to trial entry Units: Years			
median	0.7	1.4	
inter-quartile range (Q1-Q3)	0.2 to 1.4	0.2 to 3.2	-

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomised	
Subject analysis set title	Imaging study population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Excludes patients with key eligibility deviations	

Reporting group values	ITT	Imaging study population	
Number of subjects	39	36	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	2	
From 65-84 years	37	34	
85 years and over	0	0	
Age continuous			
Units: years			
median	74.5	75.1	
inter-quartile range (Q1-Q3)	72.1 to 79.5	72.8 to 79.5	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	39	36	
Weight at trial entry			
Units: Subjects			
<80kg	19	18	
>=80kg	20	18	
ALP at trial entry			
Units: Subjects			
<220 U/L	30	29	
>=220 U/L	9	7	
Prior bisphosphonate use			
Units: Subjects			
Yes	5	4	
No	34	32	
EOD grade at trial entry			
Units: Subjects			
EOD1	18	17	
EOD2	14	13	
EOD3	4	4	
EOD4	3	2	
Lymh node metastases at diagnosis			
Units: Subjects			
Yes	8	7	
No	31	29	
Gleason score at diagnosis (total)			
Units: Subjects			
Gleason 6	3	3	
Gleason 7	9	9	
Gleason 8	9	7	
Gleason 9	17	16	
Missing	1	1	
Time since histological confirmation of disease to trial entry			
Units: Years			
median	3.9	3.9	
inter-quartile range (Q1-Q3)	2.1 to 6.7	2.3 to 6.7	
Time since confirmation of bone metastases to trial entry			
Units: Years			

median	2.2	2.3	
inter-quartile range (Q1-Q3)	1.1 to 3.9	1.1 to 4.3	
Time since castration resistance to trial entry Units: Years			
median	1.1	1.0	
inter-quartile range (Q1-Q3)	0.2 to 2.4	0.1 to 2.1	

End points

End points reporting groups

Reporting group title	55 kBq/kg Radium 223
Reporting group description:	
Participants in this arm were allocated to receive 55 kBq/kg of Radium 223. Allocation ratio between the 2 arms was 1:1. Treatment allocation was via minimisation with a random element; balancing factors included patient weight, total ALP and current bisphosphonate use. Dose allocation was not blinded. Patients received treatment with radium-223 at the allocated dose via IV administration every 4 weeks for up to 6 cycles.	
Reporting group title	88 kBq/kg Radium 223
Reporting group description:	
Patients received treatment with radium-223 at the 88 kBq/kg via IV administration every 4 weeks for up to 6 cycles.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients randomised	
Subject analysis set title	Imaging study population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Excludes patients with key eligibility deviations	

Primary: DW-MRI response by global median ADC

End point title	DW-MRI response by global median ADC[1]
End point description:	
End point type	Primary
End point timeframe:	
From 1st injection until end of cycle 6.	

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: No statistical analysis was included because the primary endpoint was assessment of response rates with no formal comparison between groups.

End point values	55 kBq/kg Radium 223	88 kBq/kg Radium 223	Imaging study population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	19	17	36	
Units: Patients				
Responder	6	8	14	
Non-responder	13	9	22	

Statistical analyses

No statistical analyses for this end point

Secondary: Qualitative DW-MRI response

End point title	Qualitative DW-MRI response

End point description:

End point type	Secondary

End point timeframe:

From 1st injection up to cycle 6.

End point values	55 kBq/kg Radium 223	88 kBq/kg Radium 223	Imaging study population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	19	17	36	
Units: Patients				
Response	3	5	8	
Likely response	6	3	9	
Stable	6	4	10	
Likely progression	2	1	3	
Progression	2	4	6	

Statistical analyses

No statistical analyses for this end point

Secondary: DW-MRI response according to mean ADC in 5 target lesions

End point title	DW-MRI response according to mean ADC in 5 target lesions

End point description:

End point type	Secondary

End point timeframe:

From 1st injection until end of cycle 6.

End point values	55 kBq/kg Radium 223	88 kBq/kg Radium 223	Imaging study population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	19	17	36	
Units: Patients				
Responder	9	14	23	
Non-responder	10	3	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Best qualitative response according to Fluoride PET-CT

End point title	Best qualitative response according to Fluoride PET-CT

End point description:

End point type	Secondary

End point timeframe:

From 1st injection until end of cycle 6.

End point values	55 kBq/kg Radium 223	88 kBq/kg Radium 223	Imaging study population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	19	17	36	
Units: Patients				
Partial response	13	8	21	
Stable disease	5	7	12	
Progressive disease	1	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Best qualitative response according to Choline PET-CT

End point title	Best qualitative response according to Choline PET-CT

End point description:

End point type	Secondary

End point timeframe:

From 1st injection until end of cycle 6.

End point values	55 kBq/kg Radium 223	88 kBq/kg Radium 223	Imaging study population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	18[2]	17	35[3]	
Units: Patients				
Partial response	5	8	13	
Stable disease	12	6	18	
Progressive disease	1	3	4	

Notes:

[2] - Choline PET-CT not available for 1 patient

[3] - Choline PET-CT not available for 1 patient

Statistical analyses

No statistical analyses for this end point

Secondary: ALP response

End point title	ALP response

End point description:

Total ALP response is defined as ≥30% reduction of the blood level compared to the baseline value, assessed up to the end of treatment, confirmed by a second total-ALP value approximately 4 or more weeks later.

End point type	Secondary

End point timeframe:

Measured up to the end of treatment.

End point values	55 kBq/kg Radium 223	88 kBq/kg Radium 223	ITT	Imaging study population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	20	19	39	36
Units: Patients				
Confirmed responder	13	12	25	24
Non-responder	7	7	14	12

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ALP progression

End point title	Time to ALP progression

End point description:

Time to total ALP progression is defined as time from trial entry and first documented ALP progression. ALP progression is defined as:
- In patients with no decline from baseline, ≥25% increase from baseline at least 12 weeks from baseline;
- In patients with initial an decline from baseline, ≥25% increase from the nadir confirmed by a second value 3 or more weeks later.

End point type	Secondary

End point timeframe:

From trial entry until ALP progression

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: Months				
median (confidence interval 95%)	9.4 (7.0 to 12.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: PSA response

End point title	PSA response

End point description:

Total PSA response is defined as ≥50% reduction of the blood level compared to the baseline value, assessed up to the end of treatment, confirmed by a second total-ALP value approximately 3 or more weeks later. Cycle 1 PSA values are used as a baseline.

End point type	Secondary

End point timeframe:

Measured up to the end of treatment

End point values	55 kBq/kg Radium 223	88 kBq/kg Radium 223	ITT	Imaging study population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	20	19	39	36
Units: Patients				
Confirmed responder	2	3	5	5
Non-responder	18	16	34	31

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA progression

End point title	Time to PSA progression

End point description:

End point type	Secondary

End point timeframe:

From trial entry to PSA progression

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: Months				
median (confidence interval 95%)	4.2 (3.9 to 11.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: CTC response

End point title	CTC response

End point description:

Overall CTC response is defined as a CTC conversion (from >5 cells/7.5ml blood at baseline to <5 cells/7.5mls confirmed by 2 readings 4 weeks apart) or a CTC fall (at least 30% fall in CTCs compared to baseline).

End point type	Secondary

End point timeframe:

Measured upto the end of treatment.

End point values	55 kBq/kg Radium 223	88 kBq/kg Radium 223	ITT	Imaging study population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	11[4]	6[5]	17[6]	16[7]
Units: Patients				
Responder	5	1	6	6
Non-responder	6	5	11	10

Notes:

[4] - Patients are required to have baseline CTC>5 to be evaluable for CTC response

[5] - Patients are required to have baseline CTC>5 to be evaluable for CTC response

[6] - Patients are required to have baseline CTC>5 to be evaluable for CTC response

[7] - Patients are required to have baseline CTC>5 to be evaluable for CTC response

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From trial entry up to 4 weeks following treatment discontinuation.
Adverse reactions were recorded until 1 year post treatment.

Adverse event reporting additional description:

Any adverse events reported after baseline by at least 5% of the safety population (i.e. all those who received at least 1 dose of radium 223) are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

All patients who received at least 1 dose of Radium 223

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Pain in extremity			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 38 (97.37%)		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	5		
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	6		
Hypertension			

subjects affected / exposed	28 / 38 (73.68%)		
occurrences (all)	84		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	24 / 38 (63.16%)		
occurrences (all)	52		
Leukopenia			
subjects affected / exposed	10 / 38 (26.32%)		
occurrences (all)	18		
Lymphopenia			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	11		
Neutropenia			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	9		
Pancytopenia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	7		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 38 (23.68%)		
occurrences (all)	24		
Gait disturbance			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	3		
Oedema peripheral			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	14 / 38 (36.84%)		
occurrences (all)	23		
Dyspepsia			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	14		
Vomiting			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Renal and urinary disorders			
Lower urinary tract symptoms			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	13		
Back pain			
subjects affected / exposed	14 / 38 (36.84%)		
occurrences (all)	35		

Bone pain subjects affected / exposed occurrences (all)	15 / 38 (39.47%) 27		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 6		
Musculoskeletal pain subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 7		
Neck pain subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 6		
Pain in extremity subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 5		
Pelvic fracture subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Spinal fracture subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	9 / 38 (23.68%) 22		
Hypercholesterolaemia subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2016	Change in dose from 50kBq/kg to 55kBq/kg and from 80kBq/kg to 88kBq/kg following world-wide NIST primary reference standard revision. Inclusion criteria changed from age ≥16 years to age ≥18 years to reflect ARSAC guidance
01 October 2018	Addition of a new objective, endpoints statistical considerations and follow up schedule to investigate the incidence of fractures post radium-223. Clarification of existing statistical and imaging considerations.
15 October 2021	Inclusion of additional exploratory endpoint related to overall survival and collection of survival data beyond 1 year.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37788117