Clinical trial results:
A phase III randomized, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)

Summary

EudraCT number	2013-003438-33
Trial protocol	IT ES FI SE DE BE GB NL NO PL FR
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	19 February 2021
First version publication date	28 February 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BAY88-8223/15396

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02043678
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	31 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare, in subjects with asymptomatic or mildly symptomatic chemotherapy-naïve bone-predominant metastatic CRPC, the clinical benefit of radium-223 dichloride versus placebo in combination with abiraterone and prednisone/prednisolone.

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. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 55
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 51
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Spain: 72
Country: Number of subjects enrolled	Finland: 14
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	United Kingdom: 64
Country: Number of subjects enrolled	Italy: 52
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United States: 90
Country: Number of subjects enrolled	Israel: 59
Country: Number of subjects enrolled	Japan: 114
Country: Number of subjects enrolled	Singapore: 40

Country: Number of subjects enrolled	Brazil: 51
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Russian Federation: 29
Worldwide total number of subjects	806
EEA total number of subjects	317

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)	167
From 65 to 84 years	601
85 years and over	38

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 19 countries between 30 March 2014 (first subject first visit) and 31 October 2019 (data cut-off date).

Pre-assignment

Screening details:

Overall, 1144 subjects were screened. Of them, 338 subjects did not complete screening, 806 subjects were randomized to treatment and 786 subjects received study treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

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

Arm description:

Subjects received 6 intravenous (IV) administrations of radium-223 dichloride 50 kiloBecquerel per kilogram (kBq/kg) (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight at intervals of 4 weeks, along with oral abiraterone acetate tablets 1000 milligrams (mg) every day plus prednisone/prednisolone 5 mg twice daily (abi/pred) for 6 cycles, followed by abi/pred until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

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

Dosage and administration details:

Subjects received abiraterone acetate tablets 1000 milligrams (mg) every day until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

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

Dosage and administration details:

Subjects received 6 IV administrations of radium-223 dichloride 50 kiloBecquerel per kilogram (kBq/kg) (55 kBq/kg after implementation of NIST update) at intervals of 4 weeks.

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

Dosage and administration details:

Subjects received 5 mg prednisone/prednisolone twice daily until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

Arm title	Placebo + Abi/Pred

Arm description:

Subjects received 6 IV administrations of placebo matched to radium-223 dichloride at intervals of 4 weeks, along with abi/pred for 6 cycles, followed by abi/pred until an on-study SSE occurred (or other withdrawal criteria were met).

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:

Subjects received abiraterone acetate tablets 1000 milligrams (mg) every day until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

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

Dosage and administration details:

Subjects received 5 mg prednisone/prednisolone twice daily until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

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:

Subjects received 6 IV administrations of placebo matched to radium-223 dichloride at intervals of 4 weeks.

Number of subjects in period 1	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred
Started	401	405
Treated	390	396
Completed	0	0
Not completed	401	405
Consent withdrawn by subject	12	15
Ongoing with treatment	34	38
AE without clinical PD	51	34
Unspecified	19	16
AE with clinical progressive disease (PD)	18	18
Clinical PD	108	138
Radiological PD	91	80
Never treated	11	9
Protocol-driven decision point	56	56
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Radium-223 dichloride + Abi/Pred
Reporting group description:	
Subjects received 6 intravenous (IV) administrations of radium-223 dichloride 50 kiloBecquerel per kilogram (kBq/kg) (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight at intervals of 4 weeks, along with oral abiraterone acetate tablets 1000 milligrams (mg) every day plus prednisone/prednisolone 5 mg twice daily (abi/pred) for 6 cycles, followed by abi/pred until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).	
Reporting group title	Placebo + Abi/Pred
Reporting group description:	
Subjects received 6 IV administrations of placebo matched to radium-223 dichloride at intervals of 4 weeks, along with abi/pred for 6 cycles, followed by abi/pred until an on-study SSE occurred (or other withdrawal criteria were met).	

Reporting group values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred	Total
Number of subjects	401	405	806
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	70.9	71.4	
standard deviation	± 8.5	± 8.4	-
Sex: Female, Male Units: Subjects			
Female	0	0	0
Male	401	405	806
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	79	78	157
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	10	16	26
White	285	284	569
More than one race	0	0	0
Unknown or Not Reported	26	26	52
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	17	23	40
Not Hispanic or Latino	361	355	716
Unknown or Not Reported	23	27	50
Stage of prostate cancer at diagnosis (Tumor Node Metastasis [TNM] Classification)			
TNM staging system stands for Tumour, Node, Metastasis. Stage I: cancer is in half of one side of the prostate or less. Stage II: cancer is in more than half of one side of the prostate, completely contained within the prostate gland. Stage III: cancer has broken through the capsule of the prostate gland, and			

may have spread into tubes that carry semen. Stage IV: cancer has spread into nearby body organs, such as the back passage or bladder; or has spread to nearby lymph nodes; or has spread to other parts of the body outside the pelvis, such as the lungs or liver.			
Units: Subjects			
Missing	19	24	43
Stage I	27	18	45
Stage IIA	22	20	42
Stage IIB	34	49	83
Stage III	102	88	190
Stage IV	197	206	403
Cancer pain assessment by Brief Pain Inventory-Short Form (BPI-SF)			
The BPI-SF is a short, self-administered questionnaire with 11 items designed to evaluate the intensity of, and the impairment caused by pain. Four items measure pain intensity (pain now, average pain, worst pain, and least pain) using 0 (“no pain”) to 10 (“pain as bad as you can imagine”) numeric rating scales, and 7 items measure the level of interference with function caused by pain (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) using 0 (no interference) to 10 (complete interference) rating scales.			
Units: Subjects			
Missing	25	33	58
Asymptomatic (Worst pain score = 0)	195	198	393
Mildly Symptomatic (Worst pain score 1 - 3)	181	174	355
Gleason score at diagnosis			
The Gleason score is an indication of prognosis based on prostate pathology. The total score ranges from 2 to 10 (ie: "1+1" to "5+5") with a higher score reflecting less-differentiated tumors with worse prognosis. The total score is a sum of two numbers which are based on the microscopic appearance of cells. The first number is the score based on the dominant, cell morphology (scored 1-5) and the second number is based on the highest grade of the non-dominant cell pattern (scored 1-5).			
Units: Subjects			
Missing	15	18	33
Less than (<) 8	140	154	294
Greater than or equal to (>=) 8	246	233	479
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Eastern cooperative oncology group (ECOG) performance status: 0= Fully active, able to carry on all pre-disease performance without restriction; 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; 3= Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4= Completely disabled, cannot carry on any self-care, totally confined to bed or chair.			
Units: Subjects			
Missing	2	3	5
ECOG=0	262	281	543
ECOG=1	137	121	258
Extent of Disease			
Units: Subjects			
Normal or abnormal because of benign bone disease	2	0	2
< 6 metastases	134	141	275
6-20 metastases	175	181	356
>20 lesions but not a superscan	71	70	141
Superscan	19	13	32
Weight			
Units: Kilograms (kg)			
arithmetic mean	82.19	82.40	
standard deviation	± 16.75	± 16.01	-

Prostate-specific antigen Units: Micrograms per liter (ug/L)			
arithmetic mean	92.39	92.33	
standard deviation	± 191.62	± 328.00	-

End points

End points reporting groups

Reporting group title	Radium-223 dichloride + Abi/Pred

Reporting group description:

Subjects received 6 intravenous (IV) administrations of radium-223 dichloride 50 kiloBecquerel per kilogram (kBq/kg) (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight at intervals of 4 weeks, along with oral abiraterone acetate tablets 1000 milligrams (mg) every day plus prednisone/prednisolone 5 mg twice daily (abi/pred) for 6 cycles, followed by abi/pred until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

Reporting group title	Placebo + Abi/Pred

Reporting group description:

Subjects received 6 IV administrations of placebo matched to radium-223 dichloride at intervals of 4 weeks, along with abi/pred for 6 cycles, followed by abi/pred until an on-study SSE occurred (or other withdrawal criteria were met).

Subject analysis set title	Intent-to-treat analysis set (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Included all randomized subjects.

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

Subject analysis set description:

Included all randomized subjects who received at least one dose of any study drug.

Primary: Symptomatic Skeletal Event Free Survival (SSE-FS)

End point title	Symptomatic Skeletal Event Free Survival (SSE-FS)

End point description:

SSE-FS was defined as time (months) from randomization to the earliest of onset date of skeletal symptoms treated with external beam radiotherapy (EBRT), onset date of pathological bone fracture, onset date of spinal cord compression, procedure date of tumor-related orthopedic surgery, or death from any cause. Subjects who died without prior SSE and ≥ 13 weeks after the last SSE assessment are censored at the last SSE assessment date. Subjects alive at the survival cut-off date are censored at the last date known to be alive. Subjects with multiple events are only counted for the category in which the first event occurred. If multiple SSE (component events) occur on the same date for 1 subject, the subject is only counted into 1 category in the order of: spinal cord compression > bone fracture > orthopedic surgery > EBRT.

End point type	Primary

End point timeframe:

From randomization until first onset of on-study symptomatic skeletal event (SSE) or death, up to 47 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	401[1]	405[2]		
Units: Months				
median (confidence interval 95%)	22.3 (20.4 to 24.8)	26.0 (21.8 to 28.3)		

Notes:
[1] - ITT
[2] - ITT

Statistical analyses

Statistical analysis title	Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred
Comparison groups	Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2636
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.917
upper limit	1.374

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time (months) from the date of randomization to the date of death due to any cause. Subjects alive at the survival cut-off date were censored at the last date known to be alive. In the below table, "99999" indicates that upper limit cannot be estimated due to censored data.

End point type	Secondary

End point timeframe:

From randomization until death from any cause, up to 67 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	401[3]	405[4]		
Units: Months				
median (confidence interval 95%)	30.1 (27.5 to 33.2)	34.8 (31.5 to 37.6)		

Notes:
[3] - ITT
[4] - ITT

Statistical analyses

Statistical analysis title	Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred
Comparison groups	Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1194
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.964
upper limit	1.374

Secondary: Radiological Progression Free Survival (rPFS)

End point title	Radiological Progression Free Survival (rPFS)

End point description:

rPFS was defined as the time (months) from the date of randomization to the date of confirmed radiological progression or death (if death occurred before progression) based on independent assessment.

End point type	Secondary

End point timeframe:

From randomization until the date of confirmed radiological progression or death, up to 47 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	401[5]	405[6]		
Units: Months				
median (confidence interval 95%)	11.2 (9.1 to 11.8)	12.4 (10.8 to 14.5)		

Notes:

[5] - ITT

[6] - ITT

Statistical analyses

Statistical analysis title	Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred
Comparison groups	Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1283
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.152

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.383

Secondary: Time to Pain Progression

End point title	Time to Pain Progression

End point description:

Time to pain progression was defined as the interval from randomization to the first date a subject experienced pain progression, assessed by BPI-SF (see Baseline Characteristics) and defined as: an increase of 2 or more points in the average worst pain score (WPS) from baseline observed at 2 consecutive evaluations >= 4 weeks apart or initiation of short- or long-acting opioid use for pain for subjects with WPS 0 at baseline; an increase of 2 or more points in the average WPS from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart and an average WPS of ≥ 4 OR initiation of short- or long-acting opioid use for pain for subjects with WPS 1 to 3 at baseline. Subjects without pain progression at the end of study are censored at the last date known to have not progressed: the last evaluation date for pain scores or last visit when recorded opiate use, whichever is last. Subjects with no on-study assessment or no baseline assessment are censored at the date of randomization.

End point type	Secondary

End point timeframe:

From randomization until the date of pain progression based on pain score, up to 47 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	401[7]	405[8]		
Units: Months				
median (confidence interval 95%)	14.4 (11.1 to 20.1)	18.7 (15.4 to 23.1)		

Notes:

[7] - ITT

[8] - ITT

Statistical analyses

Statistical analysis title	Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred
Comparison groups	Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1669
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.145

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.945
upper limit	1.389

Secondary: Time to Cytotoxic Chemotherapy

End point title	Time to Cytotoxic Chemotherapy

End point description:

Time to cytotoxic chemotherapy is time (months) from randomization to the earliest date of the first cytotoxic chemotherapy. Subjects who have not started cytotoxic chemotherapy during the study were censored at the last assessment date. In the below table, "99999" indicates that upper limit cannot be estimated due to censored data.

End point type	Secondary

End point timeframe:

From randomization until the date of first cytotoxic chemotherapy, up to 47 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	401[9]	405[10]		
Units: Months				
median (confidence interval 95%)	29.5 (26.5 to 35.7)	28.5 (23.7 to 99999)		

Notes:

[9] - ITT

[10] - ITT

Statistical analyses

Statistical analysis title	Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred
Comparison groups	Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred
Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7871
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.816
upper limit	1.308

Secondary: Time to Opiate Use for Cancer Pain

End point title	Time to Opiate Use for Cancer Pain

End point description:

Time to opiate use for cancer pain was defined as the interval from the date of randomization to the date of opiate use.

End point type	Secondary

End point timeframe:

From randomization until the date of opiate use, up to 47 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398[11]	392[12]		
Units: Months				
median (confidence interval 95%)	19.0 (14.4 to 23.2)	22.6 (18.0 to 25.7)		

Notes:

[11] - ITT set excluding subjects who had opiate use at baseline

[12] - ITT set excluding subjects who had opiate use at baseline

Statistical analyses

Statistical analysis title	Radium-223 dichloride+Abi/Pred vs Placebo+Abi/Pred
Comparison groups	Radium-223 dichloride + Abi/Pred v Placebo + Abi/Pred
Number of subjects included in analysis	790
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2467
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.126
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.921
upper limit	1.378

Secondary: Number of subjects with treatment-emergent adverse events

End point title	Number of subjects with treatment-emergent adverse events

End point description:

An adverse event (AE) was any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant in the study. A serious adverse event (SAE) was any untoward medical occurrence that at any dose was resulting in death, was lifethreatening, requires hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity. AEs or SAEs occurring after start of study treatment until the end of the treatment period were defined as treatment-emergent AEs (TEAEs) or serious TEAEs. Drug-related TEAEs or serious TEAEs were those with "reasonable causal relationship" to the study treatment decided by the investigators.

End point type	Secondary

End point timeframe:

From start of study treatment until the end of the treatment period, up to 65 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392[13]	394[14]		
Units: Subjects				
Any TEAE	382	387		
Any drug-related TEAE	265	271		
Radium-223/Placebo-related TEAE	92	92		
Any serious TEAE	175	172		
Any drug-related serious TEAE	32	29		
Radium-223/Placebo-related serious TEAE	11	7		

Notes:

[13] - SAF

[14] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with radium-223/placebo-related treatment-emergent adverse events per maximum intensity

End point title	Number of subjects with radium-223/placebo-related treatment-emergent adverse events per maximum intensity

End point description:

An adverse event (AE) was any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant in the study. A serious adverse event (SAE) was any untoward medical occurrence that at any dose was resulting in death, was lifethreatening, requires hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity. AEs or SAEs occurring after start of study treatment until the end of the treatment period were defined as treatment-emergent AEs (TEAEs) or serious TEAEs. Radium-223/placebo-related TEAEs or serious TEAEs were those with "reasonable causal relationship" to radium-223 or placebo decided by the investigators.

End point type	Secondary

End point timeframe:

From start of study treatment until the end of the treatment period, up to 65 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392[15]	394[16]		
Units: Subjects				
TEAE - Grade 1	44	53		
TEAE - Grade 2	28	24		

TEAE - Grade 3	19	13		
TEAE - Grade 4	1	2		
Serious TEAE - Grade 2	3	0		
Serious TEAE - Grade 3	8	5		
Serious TEAE - Grade 4	0	2		

Notes:

[15] - SAF

[16] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any treatment-emergent additional primary malignancies

End point title	Number of subjects with any treatment-emergent additional primary malignancies

End point description:

Treatment-emergent additional primary malignancies were adverse events identified as additional primary malignancies that occurred after start of study treatment until the end of the treatment period.

End point type	Secondary

End point timeframe:

From start of study treatment until 4 weeks after last study treatment, up to 65 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392[17]	394[18]		
Units: Subjects	26	25		

Notes:

[17] - SAF

[18] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent bone fractures

End point title	Number of subjects with treatment-emergent bone fractures

End point description:

Treatment-emergent fractures were adverse events identified as fractures that occurred after start of study treatment until the end of the treatment period. All bone fractures and bone-associated events (e.g., osteoporosis) were reported as either AEs, or SAEs if the criteria of SAE were met, regardless of the investigator’s causality assessment.

End point type	Secondary

End point timeframe:

From start of study treatment until 4 weeks after last study treatment, up to 65 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392[19]	394[20]		
Units: Subjects	107	49		

Notes:

[19] - SAF

[20] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with post-treatment adverse events

End point title	Number of subjects with post-treatment adverse events

End point description:

An adverse event (AE) was any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant in the study. Any bleeding event occurring during the study was not documented as an AE because this event was planned to be captured in the assessment of efficacy. AEs that started after the treatment period were defined as post-treatment AEs. Drug-related AEs were those with "reasonable causal relationship" to the study treatment decided by the investigators.

End point type	Secondary

End point timeframe:

After the treatment period, up to 46 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392[21]	394[22]		
Units: Subjects				
Any events	138	133		
Any drug-related events	18	9		
Any chemotherapy-related events	31	34		
Any additional primary malignancies	6	7		

Notes:

[21] - SAF

[22] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any study drug-related post-treatment adverse events per maximum intensity

End point title	Number of subjects with any study drug-related post-treatment adverse events per maximum intensity

End point description:

An adverse event (AE) was any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant in the study. Any bleeding event occurring during the study was not documented as an AE because this event was

planned to be captured in the assessment of efficacy. AEs that started after the treatment period were defined as post-treatment AEs. Drug-related AEs were those with "reasonable causal relationship" to the study treatment decided by the investigators.

End point type	Secondary

End point timeframe:

After the treatment period, up to 46 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392[23]	394[24]		
Units: Subjects				
Grade 1	3	3		
Grade 2	9	3		
Grade 3	5	3		
Grade 4	1	0		

Notes:

[23] - SAF

[24] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with post-treatment chemotherapy-related blood and lymphatic system disorders

End point title	Number of subjects with post-treatment chemotherapy-related blood and lymphatic system disorders

End point description:

Post-treatment blood and lymphatic system disorders were adverse events identified as blood and lymphatic system disorders that occurred after the end of the treatment period until participant died, was lost to follow-up, withdrew informed consent, actively objected to collection of further data, or was transitioned to the extended safety follow-up study.

End point type	Secondary

End point timeframe:

After the treatment period, up to 46 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392[25]	394[26]		
Units: Subjects				
Anaemia	5	4		
Bone marrow failure	1	0		
Febrile neutropenia	5	8		
Leukopenia	1	0		
Neutropenia	8	3		

Pancytopenia	0	1		
Thrombocytopenia	2	2		

Notes:

[25] - SAF

[26] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with post-treatment bone fractures

End point title	Number of subjects with post-treatment bone fractures

End point description:

Post-treatment fractures were adverse events identified as fractures that occured after the end of the treatment period until participant died, was lost to follow-up, withdrew informed consent, actively objected to collection of further data, or was transitioned to the extended safety follow-up study. All bone fractures and bone-associated events (e.g., osteoporosis), were reported as either AEs, or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.

End point type	Secondary

End point timeframe:

After the treatment period, up to 46 months

End point values	Radium-223 dichloride + Abi/Pred	Placebo + Abi/Pred		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392[27]	394[28]		
Units: Subjects				
Lumbar vertebral fracture	0	1		
Rib fracture	0	1		
Spinal compression fracture	0	1		
Thoracic vertebral fracture	0	1		
Traumatic fracture	6	2		
Osteoporotic fracture	6	0		
Pathological fracture	12	13		

Notes:

[27] - SAF

[28] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment to cut-off date 31-OCT-2019, which is about 67 months.

Adverse event reporting additional description:

Adverse events (AEs) included any event arising or worsening from the start of the study treatment. All occurrences of additional malignancies, chemotherapy-related events, bone fractures and bone associated events were reported as AE regardless of the investigator's causality assessment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Placebo + Abi/Pred

Reporting group description:

Participants received 6 IV administrations of placebo matched to radium-223 dichloride at intervals of 4 weeks, along with abi/pred for 6 cycles, followed by abi/pred until an on-study SSE occurred (or other withdrawal criteria were met).

Reporting group title	Radium-223 dichloride + Abi/Pred

Reporting group description:

Participants received 6 intravenous (IV) administrations of radium-223 dichloride 50 kiloBecquerel per kilogram (kBq/kg) (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) body weight at intervals of 4 weeks, along with oral abiraterone acetate tablets 1000 milligrams (mg) every day plus prednisone/prednisolone 5 mg twice daily (abi/pred) for 6 cycles, followed by abi/pred until an on-study symptomatic skeletal event (SSE) occurred (or other withdrawal criteria were met).

Serious adverse events	Placebo + Abi/Pred	Radium-223 dichloride + Abi/Pred	
Total subjects affected by serious adverse events			
subjects affected / exposed	185 / 394 (46.95%)	190 / 392 (48.47%)	
number of deaths (all causes)	242	254	
number of deaths resulting from adverse events	30	34	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			

subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	6 / 394 (1.52%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 12	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer recurrent			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholangiocarcinoma			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon cancer			

subjects affected / exposed	1 / 394 (0.25%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kaposi's sarcoma			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal sinus cancer			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	7 / 394 (1.78%)	7 / 392 (1.79%)	
occurrences causally related to treatment / all	0 / 23	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer metastatic			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain neoplasm			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaplastic thyroid cancer			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal adenocarcinoma			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer metastatic			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Carcinoid tumour of the small bowel			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer metastatic			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Circulatory collapse			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 394 (1.02%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	2 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 394 (0.51%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			

subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 394 (1.02%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	13 / 394 (3.30%)	10 / 392 (2.55%)	
occurrences causally related to treatment / all	0 / 19	0 / 14	
deaths causally related to treatment / all	0 / 11	0 / 7	
Non-cardiac chest pain			

subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Death			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Physical deconditioning			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatism			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gynaecomastia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 394 (1.02%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 394 (0.51%)	6 / 392 (1.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lower respiratory tract inflammation			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			

subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 394 (0.76%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Humerus fracture			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	5 / 394 (1.27%)	13 / 392 (3.32%)	
occurrences causally related to treatment / all	1 / 5	1 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudophakic bullous keratopathy			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Inborn error of metabolism			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	4 / 394 (1.02%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Aortic valve incompetence			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arrhythmia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	8 / 394 (2.03%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	3 / 394 (0.76%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery stenosis			

subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary ostial stenosis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 394 (0.25%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sinus bradycardia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Monoplegia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			

subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	9 / 394 (2.28%)	7 / 392 (1.79%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 394 (0.51%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	2 / 394 (0.51%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal epidural haematoma			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial neuralgia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alexia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			

subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 394 (1.02%)	9 / 392 (2.30%)	
occurrences causally related to treatment / all	1 / 5	8 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 394 (1.52%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 394 (0.00%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 0	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 394 (1.27%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	2 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal achalasia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 394 (0.51%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			

subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anal prolapse			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disease			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	4 / 394 (1.02%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	4 / 394 (1.02%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	3 / 394 (0.76%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urethral stenosis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			

subjects affected / exposed	2 / 394 (0.51%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Primary adrenal insufficiency			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 394 (0.51%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	11 / 394 (2.79%)	8 / 392 (2.04%)	
occurrences causally related to treatment / all	0 / 12	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	5 / 394 (1.27%)	7 / 392 (1.79%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 394 (0.51%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal pain			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 394 (0.25%)	9 / 392 (2.30%)	
occurrences causally related to treatment / all	0 / 3	5 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	4 / 394 (1.02%)	8 / 392 (2.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			

subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 394 (0.25%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 394 (0.51%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 394 (0.51%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme disease			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	16 / 394 (4.06%)	12 / 392 (3.06%)	
occurrences causally related to treatment / all	1 / 20	0 / 15	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 394 (1.02%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 2	
Septic shock			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	5 / 394 (1.27%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	10 / 394 (2.54%)	18 / 392 (4.59%)	
occurrences causally related to treatment / all	0 / 12	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 394 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urosepsis			
subjects affected / exposed	6 / 394 (1.52%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 12	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arthritis bacterial			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis fungal			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute endocarditis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 394 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin infection			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 394 (0.25%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 394 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 394 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 394 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 11	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency			

subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 394 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Abi/Pred	Radium-223 dichloride + Abi/Pred	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	376 / 394 (95.43%)	369 / 392 (94.13%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	80 / 394 (20.30%)	61 / 392 (15.56%)	
occurrences (all)	213	164	
Hot flush			
subjects affected / exposed	51 / 394 (12.94%)	23 / 392 (5.87%)	
occurrences (all)	53	25	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	43 / 394 (10.91%)	37 / 392 (9.44%)	
occurrences (all)	60	48	
Fatigue			
subjects affected / exposed	95 / 394 (24.11%)	103 / 392 (26.28%)	
occurrences (all)	136	142	
Oedema peripheral			
subjects affected / exposed	64 / 394 (16.24%)	57 / 392 (14.54%)	
occurrences (all)	77	78	
Pyrexia			

subjects affected / exposed	34 / 394 (8.63%)	28 / 392 (7.14%)	
occurrences (all)	49	33	
Influenza like illness			
subjects affected / exposed	20 / 394 (5.08%)	12 / 392 (3.06%)	
occurrences (all)	24	16	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	21 / 394 (5.33%)	12 / 392 (3.06%)	
occurrences (all)	31	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 394 (10.41%)	36 / 392 (9.18%)	
occurrences (all)	50	42	
Dyspnoea			
subjects affected / exposed	31 / 394 (7.87%)	20 / 392 (5.10%)	
occurrences (all)	35	28	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	25 / 394 (6.35%)	32 / 392 (8.16%)	
occurrences (all)	26	35	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	61 / 394 (15.48%)	69 / 392 (17.60%)	
occurrences (all)	149	180	
Aspartate aminotransferase increased			
subjects affected / exposed	55 / 394 (13.96%)	61 / 392 (15.56%)	
occurrences (all)	104	127	
Weight decreased			
subjects affected / exposed	24 / 394 (6.09%)	20 / 392 (5.10%)	
occurrences (all)	34	32	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	50 / 394 (12.69%)	60 / 392 (15.31%)	
occurrences (all)	70	87	
Traumatic fracture			

subjects affected / exposed	23 / 394 (5.84%)	42 / 392 (10.71%)	
occurrences (all)	48	72	
Contusion			
subjects affected / exposed	31 / 394 (7.87%)	28 / 392 (7.14%)	
occurrences (all)	37	38	
Nervous system disorders			
Dizziness			
subjects affected / exposed	35 / 394 (8.88%)	45 / 392 (11.48%)	
occurrences (all)	41	54	
Headache			
subjects affected / exposed	31 / 394 (7.87%)	30 / 392 (7.65%)	
occurrences (all)	39	45	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	61 / 394 (15.48%)	65 / 392 (16.58%)	
occurrences (all)	113	134	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 394 (3.81%)	23 / 392 (5.87%)	
occurrences (all)	17	24	
Constipation			
subjects affected / exposed	79 / 394 (20.05%)	69 / 392 (17.60%)	
occurrences (all)	97	81	
Diarrhoea			
subjects affected / exposed	71 / 394 (18.02%)	69 / 392 (17.60%)	
occurrences (all)	102	107	
Dyspepsia			
subjects affected / exposed	15 / 394 (3.81%)	20 / 392 (5.10%)	
occurrences (all)	16	23	
Nausea			
subjects affected / exposed	67 / 394 (17.01%)	76 / 392 (19.39%)	
occurrences (all)	74	91	
Vomiting			
subjects affected / exposed	40 / 394 (10.15%)	40 / 392 (10.20%)	
occurrences (all)	45	48	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	21 / 394 (5.33%)	31 / 392 (7.91%)	
occurrences (all)	28	44	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	88 / 394 (22.34%)	91 / 392 (23.21%)	
occurrences (all)	155	133	
Back pain			
subjects affected / exposed	138 / 394 (35.03%)	151 / 392 (38.52%)	
occurrences (all)	209	250	
Bone pain			
subjects affected / exposed	76 / 394 (19.29%)	69 / 392 (17.60%)	
occurrences (all)	100	96	
Muscle spasms			
subjects affected / exposed	30 / 394 (7.61%)	27 / 392 (6.89%)	
occurrences (all)	34	32	
Muscular weakness			
subjects affected / exposed	36 / 394 (9.14%)	25 / 392 (6.38%)	
occurrences (all)	50	39	
Musculoskeletal pain			
subjects affected / exposed	47 / 394 (11.93%)	46 / 392 (11.73%)	
occurrences (all)	58	55	
Myalgia			
subjects affected / exposed	23 / 394 (5.84%)	25 / 392 (6.38%)	
occurrences (all)	26	29	
Neck pain			
subjects affected / exposed	24 / 394 (6.09%)	17 / 392 (4.34%)	
occurrences (all)	30	18	
Osteoporosis			
subjects affected / exposed	1 / 394 (0.25%)	27 / 392 (6.89%)	
occurrences (all)	1	28	
Osteoporotic fracture			
subjects affected / exposed	1 / 394 (0.25%)	26 / 392 (6.63%)	
occurrences (all)	1	75	
Pain in extremity			

subjects affected / exposed	58 / 394 (14.72%)	52 / 392 (13.27%)	
occurrences (all)	80	73	
Pathological fracture			
subjects affected / exposed	26 / 394 (6.60%)	48 / 392 (12.24%)	
occurrences (all)	40	68	
Musculoskeletal chest pain			
subjects affected / exposed	31 / 394 (7.87%)	28 / 392 (7.14%)	
occurrences (all)	39	41	
Spinal pain			
subjects affected / exposed	27 / 394 (6.85%)	30 / 392 (7.65%)	
occurrences (all)	34	35	
Infections and infestations			
Influenza			
subjects affected / exposed	13 / 394 (3.30%)	22 / 392 (5.61%)	
occurrences (all)	21	23	
Nasopharyngitis			
subjects affected / exposed	38 / 394 (9.64%)	31 / 392 (7.91%)	
occurrences (all)	53	40	
Upper respiratory tract infection			
subjects affected / exposed	33 / 394 (8.38%)	28 / 392 (7.14%)	
occurrences (all)	43	39	
Urinary tract infection			
subjects affected / exposed	31 / 394 (7.87%)	39 / 392 (9.95%)	
occurrences (all)	38	54	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	43 / 394 (10.91%)	43 / 392 (10.97%)	
occurrences (all)	75	76	
Decreased appetite			
subjects affected / exposed	52 / 394 (13.20%)	65 / 392 (16.58%)	
occurrences (all)	54	82	
Hyperglycaemia			
subjects affected / exposed	23 / 394 (5.84%)	12 / 392 (3.06%)	
occurrences (all)	50	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2014	Amendment 1 (integrated protocol Version 2.0) specified the following key modifications: 1. Modified the inclusion criterion to clarify the permitted age range. 2. Modified the inclusion criterion to expand the permitted estimated GFR. 3. Clarified study treatment is either radium-223 dichloride (Arm A) or placebo (Arm B). 4. Clarified the maximum radium-223 dichloride treatment duration. 7. Clarified that abiraterone is not considered study medication after an on-study SSE. 8. Clarified he process for maintaining the blind. 9. Corrected the hemoglobin level that must be met for dosing. 10. Added collection of SSEs during the screening period. 11. Clarified that survival status would be collected throughout the study. 12. Clarified that collection of cancer-related treatments includes androgen synthesis inhibitors/androgen receptor antagonists and excludes analgesics. 13. Added the modified RECIST v1.1 criteria.
11 June 2015	Amendment 2 (integrated protocol Version 3.0) specified the following key modifications: 1. Updated dosing and dose calibration of radium-223 dichloride to reflect revised NIST standardization for radium-223. 2. Removed cytological confirmation of adenocarcinoma of the prostate from inclusion criteria; histological confirmation only. 3. Clarified that the treatment period ended when a subject received abiraterone/prednisone as the standard of care (non-IMP) after an SSE. 4. Added an exclusion for immunotherapy (e.g., sipuleucel-T) within 4 weeks before the first dose of radium-223 dichloride. 5. Clarified duration of prohibited concomitant therapy was from screening onwards. 6. Clarified potassium requirement for ECG collection.
12 September 2016	Amendment 4 (integrated protocol Version 4.0) specified the following key modifications: 1. Clarified continuation of medical castration. 2. Clarified documentation of radiological progression. 3. Clarified study drug handling if administration was postponed more than 3 days. 4. Clarified treatment unblinding procedures. 5. Removed bisphosphonate timing requirements.
02 April 2018	Amendment 6 (integrated protocol Version 5.0) specified the following modifications: 1. Requested that bone fractures and bone-associated events (e.g., osteoporosis) were to be reported as (S)AEs, including during long-term follow-up, regardless of the investigator's causality assessment. 2. Added an independent radiological review of fractures. 3. Added that radium-223 dichloride should not be given in combination with abiraterone plus prednisone/prednisolone during follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Occurrence of "±" in relation with standard deviation is auto generated. Decimal places were automatically truncated if last decimals is equals to zero.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30738780