



Clinical trial results:

PREVAIL: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naive Patients with Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy

Summary

EudraCT number	2010-020821-41
Trial protocol	DE BE GB NL ES SE AT FI DK SK IT LT
Global end of trial date	

Results information

Result version number	v1
This version publication date	20 October 2016
First version publication date	18 July 2015

Trial information

Trial identification

Sponsor protocol code	MDV3100-03
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01212991
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medivation, Inc.
Sponsor organisation address	525 Market St., San Francisco, United States, 94105
Public contact	Phillip Cole, MD, Medivation, Inc., phillip.cole@medivation.com
Scientific contact	Phillip Cole, MD, Medivation, Inc., phillip.cole@medivation.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	16 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 September 2013
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine the benefit of enzalutamide versus placebo as assessed by overall survival and radiographic progression-free survival in patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy and had not yet received cytotoxic chemotherapy.

Protection of trial subjects:

This study was conducted in conformance with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research was conducted, whichever provided greater protection of the individual. In addition, the study was conducted using Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines. Specifically, this study was based on adequately performed laboratory and animal experimentation; the study was conducted under a protocol reviewed and approved by an IRB/IEC; the study was conducted by scientifically and medically qualified persons; the benefits of the study were in proportion to the risks; the rights and welfare of the patients were respected; the physicians conducting the study did not find the hazards to outweigh the potential benefits.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 247
Country: Number of subjects enrolled	Slovakia: 27
Country: Number of subjects enrolled	Finland: 33
Country: Number of subjects enrolled	Spain: 81
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	United Kingdom: 153
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	France: 175
Country: Number of subjects enrolled	Canada: 179
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Belgium: 57

Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	Australia: 232
Country: Number of subjects enrolled	Denmark: 87
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	Germany: 83
Country: Number of subjects enrolled	Japan: 61
Country: Number of subjects enrolled	Sweden: 39
Country: Number of subjects enrolled	Korea, Republic of: 78
Worldwide total number of subjects	1717
EEA total number of subjects	864

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)	358
From 65 to 84 years	1264
85 years and over	95

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were randomized 1:1 to receive either enzalutamide or placebo.

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

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	Enzalutamide
------------------	--------------

Arm description:

Patients received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.

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

Dosage and administration details:

Patients received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.

Arm title	Placebo
------------------	---------

Arm description:

Patients received placebo, administered as four capsules, once per day by mouth.

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

Dosage and administration details:

Patients received placebo, administered as four capsules, once per day by mouth.

Number of subjects in period 1	Enzalutamide	Placebo
Started	872	845
Completed	259	471
Not completed	613	374
Consent withdrawn by subject	4	14
Death	241	299

Continuing Treatment	367	61
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Enzalutamide
Reporting group description:	
Patients received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.	
Reporting group title	Placebo
Reporting group description:	
Patients received placebo, administered as four capsules, once per day by mouth.	

Reporting group values	Enzalutamide	Placebo	Total
Number of subjects	872	845	1717
Age Categorical			
Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	179	179	358
>=65 years	693	666	1359
Age Continuous			
Units: years			
arithmetic mean	71.3	71.2	
standard deviation	± 8.51	± 8.42	-
Gender, Male/Female			
Units: participants			
Male	872	845	1717
Region of Enrollment			
Units: Subjects			
United States	127	120	247
Slovakia	13	14	27
Finland	18	15	33
Spain	44	37	81
Lithuania	8	6	14
Austria	9	9	18
Russian Federation	12	10	22
Israel	14	11	25
United Kingdom	78	75	153
Italy	15	15	30
France	85	90	175
Canada	91	88	179
Poland	21	18	39
Belgium	28	29	57
Singapore	5	4	9
Australia	116	116	232
Denmark	43	44	87
Netherlands	15	13	28
Germany	41	42	83
Japan	28	33	61
Sweden	21	18	39
Korea, Republic of	40	38	78

End points

End points reporting groups

Reporting group title	Enzalutamide
Reporting group description: Patients received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.	
Reporting group title	Placebo
Reporting group description: Patients received placebo, administered as four capsules, once per day by mouth.	
Subject analysis set title	Intent-to-treat: Radiographic Progression-free Survival
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All patients randomly assigned to treatment excluding 84 patients who were not randomized before the radiographic progression-free survival data cutoff date of 06 May 2012.	
Subject analysis set title	Evaluable Intent-to-treat Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All patients randomly assigned to treatment with PSA values at baseline and at least one postbaseline assessment.	
Subject analysis set title	Intent-to-treat With Measurable Disease
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All participants who were randomly assigned to treatment and had at least one target lesion at screening.	
Subject analysis set title	Intent-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomly assigned to treatment.	

Primary: Overall Survival

End point title	Overall Survival
End point description: Overall survival was defined as the time from randomization to death due to any cause. For patients who were alive at the time of the analysis data cutoff, overall survival was censored at the last date the patient was known to be alive or analysis data cutoff date, whichever was first. This included patients who were known to have died after the data analysis cutoff date. Patients with no post-baseline survival information were censored on the date of randomization. '99999' indicates that the upper limit of the 95% confidence interval was not calculable because an insufficient number of patients reached the event at the final time point for assessment.	
End point type	Primary
End point timeframe: During study period (up to 3 years)	

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	872 ^[1]	845 ^[2]		
Units: months				
median (confidence interval 95%)	32.4 (30.1 to 99999)	30.2 (28 to 99999)		

Notes:

[1] - Intent-to-treat

[2] - Intent-to-treat

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.706
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.596
upper limit	0.837

Notes:

[3] - A 2-stage group-sequential method (Lan DeMets OBF) assigned the level of significance for the pre-specified interim overall survival analysis ($p < 0.015$) based on overall 2-sided type I error rate of 0.049. Final results based upon interim analysis.

Primary: Radiographic Progression-free Survival

End point title	Radiographic Progression-free Survival
End point description:	
Radiographic progression-free survival (rPFS) was defined as the time from randomization to the first objective evidence of radiographic disease progression (rDP) assessed by blinded independent central radiology review or death due to any cause within 168 days after treatment discontinuation, whichever was first. RDP was evaluated by CT scan or MRI and radionuclide bone scans at regularly scheduled visits. RDP in bone required a confirmatory scan. RDP in soft tissue did not require a confirmatory scan for purposes of analysis. RDP was evaluated using RECIST 1.1 for soft tissue disease and PCWG2 guidelines for bone disease. Patients who did not reach the endpoint were censored at their last assessment.	
'99999' indicates the median time to rPFS and its upper 95% confidence limit were not yet reached in the enzalutamide group because an insufficient number of patients had an event at the time of analysis.	
End point type	Primary
End point timeframe:	
During study period (up to 20 months)	

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	832 ^[4]	801 ^[5]		
Units: months				
median (confidence interval 95%)	99999 (13.8 to 99999)	3.9 (3.7 to 5.4)		

Notes:

[4] - Intent-to-treat: Radiographic Progression-free Survival

[5] - Intent-to-treat: Radiographic Progression-free Survival

Statistical analyses

Statistical analysis title	Radiographic Progression-free Survival
Comparison groups	Placebo v Enzalutamide
Number of subjects included in analysis	1633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.186
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.149
upper limit	0.231

Notes:

[6] - The assigned 2-sided type I error rate was 0.001 for the analysis of radiographic progression-free survival.

Secondary: Time to First Skeletal-related Event

End point title	Time to First Skeletal-related Event
-----------------	--------------------------------------

End point description:

Time to first skeletal-related event (SRE) was defined as the time from randomization to the date of the first occurrence of an SRE for each patient. An SRE was defined as radiation therapy or surgery to bone for prostate cancer, pathological bone fracture, spinal cord compression, or initiation/change in antineoplastic therapy to treat bone pain from prostate cancer. SREs were recorded at each scheduled and unscheduled study visit and during long-term follow-up if an SRE was not documented previously. Patients who did not have an SRE at the time of the analysis data cutoff were censored at the date of last assessment indicating no evidence of SRE. Patients with no postbaseline assessments were censored on the date of randomization.

'99999' indicates that the upper limit of the 95% confidence interval was not calculable because an insufficient number of patients reached the event at the final time point for assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

During study period (up to 3 years)

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	872 ^[7]	845 ^[8]		
Units: months				
median (confidence interval 95%)	31.1 (29.5 to 99999)	31.3 (23.9 to 99999)		

Notes:

[7] - Intent-to-treat

[8] - Intent-to-treat

Statistical analyses

Statistical analysis title	Time to First Skeletal-related Event
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.718
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.844

Notes:

[9] - The Holm step down method of multiple comparisons was used to maintain a study-wide type I error of 5% for prespecified secondary efficacy analyses. The 2-sided type I error rate was 0.01 for this analysis.

Secondary: Time to Initiation of Cytotoxic Chemotherapy

End point title	Time to Initiation of Cytotoxic Chemotherapy
-----------------	--

End point description:

The time to initiation of cytotoxic chemotherapy was defined as the time from randomization to the date of initiation of cytotoxic chemotherapy for the treatment of prostate cancer for each patient. For patients who did not start cytotoxic chemotherapy at the time of the analysis data cutoff, time to initiation of cytotoxic chemotherapy was censored at the date of last assessment where no cytotoxic chemotherapy was indicated or at the analysis data cutoff date, whichever was first. Time to initiation of cytotoxic chemotherapy for patients with no postbaseline assessments was censored on the date of randomization.

'99999' indicates that the upper limit of the 95% confidence interval was not calculable because an insufficient number of patients in the enzalutamide group reached the event at the final time point for assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

During study period (up to 3 years)

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	872 ^[10]	845 ^[11]		
Units: months				
median (confidence interval 95%)	28 (25.8 to 99999)	10.8 (9.7 to 12.2)		

Notes:

[10] - Intent-to-treat

[11] - Intent-to-treat

Statistical analyses

Statistical analysis title	Time to Initiation of Cytotoxic Chemotherapy
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.349
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.303
upper limit	0.403

Notes:

[12] - The Holm step down method of multiple comparisons was used to maintain a study wide type I error of 5% for prespecified secondary efficacy analyses. The 2-sided type I error rate was 0.0125 for this analysis.

Secondary: Time to Prostate-specific Antigen (PSA) Progression

End point title	Time to Prostate-specific Antigen (PSA) Progression
End point description:	Time to PSA progression was defined as the time from randomization to date of first confirmed observation of PSA progression for each patient. For patients with PSA declines at week 13, the PSA progression date was defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir was documented, and confirmed 3 or more weeks later. For patients with no PSA decline at week 13, the PSA progression date was defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above baseline was documented, and confirmed 3 or more weeks later. For patients who did not have confirmed PSA progression at the time of the analysis data cutoff, time to PSA progression was censored at the date of the last PSA assessment showing no evidence of confirmed PSA progression or the analysis data cutoff date, whichever was first. Time to PSA progression for patients with no postbaseline assessments was censored on the date of randomization.
End point type	Secondary
End point timeframe:	
During study period (up to 3 years)	

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	872 ^[13]	845 ^[14]		
Units: months				
median (confidence interval 95%)	11.2 (11.1 to 13.7)	2.8 (2.8 to 2.9)		

Notes:

[13] - Intent-to-treat

[14] - Intent-to-treat

Statistical analyses

Statistical analysis title	Time to PSA Progression
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.169
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.147
upper limit	0.195

Notes:

[15] - The Holm step down method of multiple comparisons was used to maintain a study wide type I error of 5% for prespecified secondary efficacy analyses. The 2-sided type I error rate was 0.0167 for this analysis.

Secondary: Percentage of Patients With Prostate Specific Antigen (PSA) Response ≥ 50%

End point title	Percentage of Patients With Prostate Specific Antigen (PSA) Response ≥ 50%
-----------------	--

End point description:

PSA response was defined as a ≥ 50% reduction in PSA from baseline to the lowest postbaseline PSA value and required confirmation by a consecutive assessment at least 3 weeks later. Patients were evaluable for PSA response rate if a patient had a PSA level measured at baseline and at least one postbaseline assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

During study period (up to 3 years)

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	854 ^[16]	777 ^[17]		
Units: Percentage of Participants				
number (confidence interval 95%)	78 (75.1 to 80.7)	3.5 (2.3 to 5)		

Notes:

[16] - Evaluable Intent-to-treat Population

[17] - Evaluable Intent-to-treat Population

Statistical analyses

Statistical analysis title	Percentage of Patients With PSA Response \geq 50%
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1631
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rates
Point estimate	74.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	71.45
upper limit	77.57

Notes:

[18] - The Holm step down method of multiple comparisons was used to maintain a study wide type I error of 5% for prespecified secondary efficacy analyses. The 2-sided type I error rate was 0.025 for this analysis.

Secondary: Best Overall Soft Tissue Response

End point title	Best Overall Soft Tissue Response
End point description:	
The best overall soft tissue objective response was defined as partial response [PR] or complete response [CR] while on study treatment based on investigator assessments of target, nontarget, and new lesions using RECIST 1.1. Soft tissue was assessed by CT or MRI at regularly scheduled visits. Only patients with measurable soft tissue disease (ie, at least 1 target lesion identified per RECIST 1.1) at screening are included in this analysis. All percentages are based on number of patients with measurable soft tissue disease at screening in each treatment group.	
End point type	Secondary
End point timeframe:	
During study period (up to 3 years)	

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396 ^[19]	381 ^[20]		
Units: Percentage of participants				
number (not applicable)	58.8	5		

Notes:

[19] - Intent-to-treat With Measurable Disease

[20] - Intent-to-treat With Measurable Disease

Statistical analyses

Statistical analysis title	Best Overall Soft Tissue Response
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	777
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in objective response rate
Point estimate	53.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	48.53
upper limit	59.17

Notes:

[21] - The Holm step down method of multiple comparisons was used to maintain a study wide type I error of 5% for prespecified secondary efficacy analyses. The 2-sided type I error rate was 0.05 for this analysis.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of time from the date of the first dose of study drug to 28 days after last dose of study drug or 1 day before the date of initiation of cytotoxic chemotherapy or an investigational agent for prostate cancer, whichever was first.

Adverse event reporting additional description:

Safety population (patients at risk) was defined as patients that received at least 1 dose of study drug. 1717 patients were randomly assigned 1:1 to treatment with enzalutamide (872 patients) or placebo (845 patients), however only 1715 patients received at least 1 dose of enzalutamide (871 patients) or placebo (844 patients).

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Enzalutamide
-----------------------	--------------

Reporting group description:

Patients received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Patients received placebo, administered as four capsules, once per day by mouth.

Serious adverse events	Enzalutamide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	279 / 871 (32.03%)	226 / 844 (26.78%)	
number of deaths (all causes)	241	299	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	17 / 871 (1.95%)	17 / 844 (2.01%)	
occurrences causally related to treatment / all	0 / 20	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	3 / 844 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant pleural effusion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to soft tissue alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Rectal cancer alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prostate cancer alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 1	1 / 844 (0.12%) 0 / 1 0 / 0		
Tonsil cancer alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 871 (0.23%) 0 / 2 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Adenocarcinoma gastric alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Anal cancer alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 871 (0.00%) 0 / 0 0 / 0	1 / 844 (0.12%) 0 / 1 0 / 0		
Bladder cancer alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Bladder transitional cell carcinoma alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Colon cancer alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal adenocarcinoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (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			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bladder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to bone marrow alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Metastases to breast alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Metastases to lung alternative dictionary used: MedDRA 16.1 subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Metastases to peritoneum alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Neuroendocrine carcinoma of the skin alternative dictionary used: MedDRA 16.1 subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Osteosarcoma alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal cell carcinoma alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer limited stage alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour embolism alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tumour pain alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal stromal tumour alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 871 (0.46%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 871 (0.46%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Aortic aneurysm rupture alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Circulatory collapse alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Hypovolaemic shock alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lymphoedema alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vena cava thrombosis alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Aortic stenosis alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Phlebitis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 871 (0.00%) 0 / 0 0 / 0	 1 / 844 (0.12%) 0 / 1 0 / 0	
Subclavian artery stenosis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0	
Surgical and medical procedures Cancer hormonal therapy alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0	
Pain management alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 871 (0.00%) 0 / 0 0 / 0	 1 / 844 (0.12%) 0 / 1 0 / 0	
General disorders and administration site conditions General physical health deterioration alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 14 / 871 (1.61%) 0 / 14 0 / 9	 10 / 844 (1.18%) 0 / 10 0 / 4	
Disease progression alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 3 / 871 (0.34%) 0 / 3 0 / 3	 7 / 844 (0.83%) 0 / 7 0 / 6	
Death			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 871 (0.46%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
Oedema peripheral			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	3 / 844 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 871 (0.46%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Generalised oedema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0		
Oedema alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 1 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0		
Sudden death alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 871 (0.00%) 0 / 0 0 / 0	 1 / 844 (0.12%) 0 / 1 0 / 1		
Suprapubic pain alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 871 (0.00%) 0 / 0 0 / 0	 1 / 844 (0.12%) 0 / 1 0 / 0		
Adverse drug reaction alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0		
Device occlusion alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 871 (0.00%) 0 / 0 0 / 0	 1 / 844 (0.12%) 0 / 2 0 / 0		
Local swelling alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (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			
Benign prostatic hyperplasia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic obstruction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 871 (0.57%)	7 / 844 (0.83%)	
occurrences causally related to treatment / all	0 / 5	3 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	3 / 844 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epistaxis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 871 (0.00%) 0 / 0 0 / 0	1 / 844 (0.12%) 0 / 1 0 / 0		
Nasal polyps alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Organising pneumonia alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 1 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Pneumonia aspiration alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Pneumonitis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Pulmonary haemorrhage alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 871 (0.00%) 0 / 0 0 / 0	1 / 844 (0.12%) 1 / 1 1 / 1		
Restrictive pulmonary disease alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction extrinsic alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (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 alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	4 / 844 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram QT prolonged alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriogram coronary alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulation time prolonged alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eastern cooperative oncology group performance status worsened			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram repolarisation abnormality			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (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			
Fall			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	7 / 871 (0.80%)	3 / 844 (0.36%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 871 (0.57%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Humerus fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Toxicity to various agents			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis radiation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Facial bones fracture alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Foreign body alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Gastroenteritis radiation alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Hand fracture alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 871 (0.00%) 0 / 0 0 / 0	1 / 844 (0.12%) 0 / 1 0 / 0		
Head injury alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0		
Lumbar vertebral fracture alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 871 (0.00%) 0 / 0 0 / 0	1 / 844 (0.12%) 0 / 1 0 / 0		
Post procedural haemorrhage alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation oesophagitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skeletal injury			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Traumatic intracranial haemorrhage alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media reaction alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	6 / 871 (0.69%)	6 / 844 (0.71%)	
occurrences causally related to treatment / all	2 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac arrest alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Myocardial infarction alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	3 / 871 (0.34%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 871 (0.46%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arteriosclerosis coronary artery alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Atrioventricular block alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina unstable alternative dictionary used: MedDRA 16.1 subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac failure acute alternative dictionary used: MedDRA 16.1 subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac failure congestive alternative dictionary used: MedDRA 16.1 subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Cardiopulmonary failure alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Congestive cardiomyopathy alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hypertensive heart disease alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Sick sinus syndrome alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal cord compression alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	28 / 871 (3.21%)	24 / 844 (2.84%)	
occurrences causally related to treatment / all	0 / 29	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	6 / 871 (0.69%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 871 (0.46%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cauda equina syndrome alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 871 (0.46%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	3 / 844 (0.36%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Paraparesis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 1 / 844 (0.12%) 0 / 1 0 / 0		
Ataxia alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0		
Brain injury alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 871 (0.00%) 0 / 0 0 / 0	 1 / 844 (0.12%) 0 / 1 0 / 1		
Cerebral haemorrhage alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 871 (0.00%) 0 / 0 0 / 0	 1 / 844 (0.12%) 0 / 1 0 / 0		
Cerebral infarction alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0		
Cervicobrachial syndrome alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0		
Coma hepatic alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Dementia				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lethargy				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Memory impairment				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Meningorrhagia				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Metabolic encephalopathy				
alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Reversible ischaemic neurological deficit				
alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord ischaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vith nerve disorder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex partial seizures			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	14 / 871 (1.61%)	8 / 844 (0.95%)	
occurrences causally related to treatment / all	1 / 19	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Iron deficiency anaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (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			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Amaurosis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 871 (0.00%) 0 / 0 0 / 0	1 / 844 (0.12%) 0 / 1 0 / 0	
Cataract alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0	
Retinal artery occlusion alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0	
Gastrointestinal disorders Constipation alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 871 (0.46%) 0 / 4 0 / 0	5 / 844 (0.59%) 0 / 6 0 / 0	
Vomiting alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 871 (0.23%) 0 / 2 0 / 0	2 / 844 (0.24%) 2 / 3 0 / 0	
Diarrhoea alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 871 (0.34%) 2 / 3 0 / 0	1 / 844 (0.12%) 1 / 1 0 / 0	
Nausea alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	3 / 871 (0.34%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 4	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Upper gastrointestinal haemorrhage alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	3 / 871 (0.34%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal pain alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrointestinal haemorrhage alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 1	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Inguinal hernia alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intestinal obstruction alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 1		
Melaena alternative dictionary used: MedDRA 16.1				
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Small intestinal obstruction alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Duodenal ulcer haemorrhage alternative dictionary used: MedDRA 16.1 subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal pain lower alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Diverticulum intestinal haemorrhagic alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dysphagia alternative dictionary used: MedDRA 16.1 subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastric ulcer haemorrhage alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Large intestinal haemorrhage alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal stenosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Duodenal ulcer alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders Bile duct obstruction alternative dictionary used: MedDRA 16.1 subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis alternative dictionary used: MedDRA 16.1 subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic alternative dictionary used: MedDRA 16.1 subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure alternative dictionary used: MedDRA 16.1 subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic function abnormal alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	10 / 871 (1.15%)	13 / 844 (1.54%)	
occurrences causally related to treatment / all	0 / 13	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 871 (0.57%)	12 / 844 (1.42%)	
occurrences causally related to treatment / all	0 / 9	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	7 / 871 (0.80%)	8 / 844 (0.95%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	11 / 844 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure acute			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 871 (0.57%)	5 / 844 (0.59%)	
occurrences causally related to treatment / all	3 / 5	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Ureteric obstruction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 871 (0.46%)	4 / 844 (0.47%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	6 / 844 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	

Bladder outlet obstruction alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 871 (0.23%) 0 / 2 0 / 0	3 / 844 (0.36%) 0 / 5 0 / 0		
Postrenal failure alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	3 / 844 (0.36%) 2 / 4 0 / 1		
Urinary bladder haemorrhage alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 871 (0.34%) 0 / 3 0 / 1	0 / 844 (0.00%) 0 / 0 0 / 0		
Calculus bladder alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 2 0 / 0	1 / 844 (0.12%) 0 / 1 0 / 0		
Prerenal failure alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	1 / 844 (0.12%) 0 / 1 0 / 0		
Renal failure alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	1 / 844 (0.12%) 0 / 1 0 / 0		
Acute prerenal failure alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder obstruction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral meatus stenosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral obstruction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine flow decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bladder neck obstruction alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0	
Micturition urgency alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 871 (0.00%) 0 / 0 0 / 0	1 / 844 (0.12%) 0 / 1 0 / 0	
Endocrine disorders Adrenal insufficiency alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 871 (0.00%) 0 / 0 0 / 0	1 / 844 (0.12%) 0 / 1 0 / 0	
Goitre alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0	
Inappropriate antidiuretic hormone secretion alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 871 (0.11%) 0 / 1 0 / 0	0 / 844 (0.00%) 0 / 0 0 / 0	
Musculoskeletal and connective tissue disorders Pathological Fracture alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	10 / 871 (1.15%) 0 / 10 0 / 0	5 / 844 (0.59%) 0 / 5 0 / 0	
Back pain			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 871 (0.46%)	5 / 844 (0.59%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	5 / 844 (0.59%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	3 / 844 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myopathy alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 871 (0.00%) 0 / 0 0 / 0	 1 / 844 (0.12%) 0 / 1 0 / 0		
Periostitis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 871 (0.00%) 0 / 0 0 / 0	 1 / 844 (0.12%) 0 / 1 0 / 0		
Rhabdomyolysis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0		
Spinal osteoarthritis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0		
Arthritis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 871 (0.11%) 0 / 1 0 / 0	 0 / 844 (0.00%) 0 / 0 0 / 0		
Groin pain alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 871 (0.00%) 0 / 0 0 / 0	 1 / 844 (0.12%) 0 / 1 0 / 0		
Pain in extremity alternative dictionary used: MedDRA 16.1				

subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	10 / 871 (1.15%)	6 / 844 (0.71%)	
occurrences causally related to treatment / all	0 / 13	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	6 / 871 (0.69%)	5 / 844 (0.59%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 871 (0.57%)	3 / 844 (0.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	4 / 844 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 871 (0.34%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	2 / 871 (0.23%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacteraemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder abscess			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis staphylococcal			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection fungal alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (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			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	3 / 844 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	2 / 844 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 871 (0.23%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fluid retention			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 871 (0.00%)	1 / 844 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 871 (0.11%)	0 / 844 (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	Enzalutamide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	844 / 871 (96.90%)	787 / 844 (93.25%)	
Vascular disorders			
Hot flush			
alternative dictionary used: MedDRA 16.1			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypertension</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>157 / 871 (18.03%)</p> <p>166</p> <p>117 / 871 (13.43%)</p> <p>158</p>	<p>65 / 844 (7.70%)</p> <p>66</p> <p>35 / 844 (4.15%)</p> <p>41</p>	
<p>General disorders and administration site conditions</p> <p>Fatigue</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Asthenia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oedema peripheral</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>310 / 871 (35.59%)</p> <p>404</p> <p>113 / 871 (12.97%)</p> <p>195</p> <p>92 / 871 (10.56%)</p> <p>115</p>	<p>218 / 844 (25.83%)</p> <p>262</p> <p>67 / 844 (7.94%)</p> <p>77</p> <p>69 / 844 (8.18%)</p> <p>83</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>72 / 871 (8.27%)</p> <p>82</p> <p>69 / 871 (7.92%)</p> <p>82</p>	<p>58 / 844 (6.87%)</p> <p>62</p> <p>60 / 844 (7.11%)</p> <p>66</p>	
<p>Psychiatric disorders</p> <p>Insomnia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>70 / 871 (8.04%)</p> <p>75</p>	<p>47 / 844 (5.57%)</p> <p>47</p>	
Investigations			

Weight decreased alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	100 / 871 (11.48%) 111	71 / 844 (8.41%) 83	
Injury, poisoning and procedural complications Fall alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	101 / 871 (11.60%) 129	45 / 844 (5.33%) 48	
Nervous system disorders Headache alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) Dizziness alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) Dysgeusia alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	91 / 871 (10.45%) 121 76 / 871 (8.73%) 87 66 / 871 (7.58%) 72	59 / 844 (6.99%) 69 53 / 844 (6.28%) 58 31 / 844 (3.67%) 31	
Blood and lymphatic system disorders Anaemia alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	66 / 871 (7.58%) 105	69 / 844 (8.18%) 113	
Gastrointestinal disorders Nausea alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) Constipation alternative dictionary used: MedDRA 16.1	201 / 871 (23.08%) 253	190 / 844 (22.51%) 217	

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>193 / 871 (22.16%)</p> <p>229</p> <p>142 / 871 (16.30%)</p> <p>187</p> <p>59 / 871 (6.77%)</p> <p>70</p> <p>46 / 871 (5.28%)</p> <p>50</p>	<p>145 / 844 (17.18%)</p> <p>169</p> <p>119 / 844 (14.10%)</p> <p>155</p> <p>70 / 844 (8.29%)</p> <p>93</p> <p>33 / 844 (3.91%)</p> <p>47</p>	
<p>Renal and urinary disorders</p> <p>Haematuria</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pollakiuria</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>73 / 871 (8.38%)</p> <p>113</p> <p>50 / 871 (5.74%)</p> <p>58</p>	<p>49 / 844 (5.81%)</p> <p>65</p> <p>37 / 844 (4.38%)</p> <p>40</p>	
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>alternative dictionary used: MedDRA 16.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>alternative dictionary used: MedDRA 16.1</p>	<p>235 / 871 (26.98%)</p> <p>329</p> <p>177 / 871 (20.32%)</p> <p>272</p>	<p>187 / 844 (22.16%)</p> <p>272</p> <p>135 / 844 (16.00%)</p> <p>186</p>	

subjects affected / exposed	102 / 871 (11.71%)	97 / 844 (11.49%)	
occurrences (all)	138	124	
Bone pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	80 / 871 (9.18%)	116 / 844 (13.74%)	
occurrences (all)	102	142	
Musculoskeletal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	87 / 871 (9.99%)	73 / 844 (8.65%)	
occurrences (all)	108	89	
Musculoskeletal chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	59 / 871 (6.77%)	43 / 844 (5.09%)	
occurrences (all)	69	53	
Myalgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	52 / 871 (5.97%)	49 / 844 (5.81%)	
occurrences (all)	64	60	
Infections and infestations			
Urinary tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	58 / 871 (6.66%)	58 / 844 (6.87%)	
occurrences (all)	82	73	
Nasopharyngitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	62 / 871 (7.12%)	42 / 844 (4.98%)	
occurrences (all)	71	45	
Upper respiratory tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	53 / 871 (6.08%)	30 / 844 (3.55%)	
occurrences (all)	65	38	
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	158 / 871 (18.14%)	136 / 844 (16.11%)	
occurrences (all)	190	164	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2010	The main purpose of this amendment was to specify that there would be a formal interim analysis and a primary analysis for overall survival. The primary analysis of overall survival would be performed when at least a total of 888 deaths were reported. Furthermore, it was specified that an unstratified log-rank test would be used to compare the MDV3100-treated and the placebo groups for both the interim and final analyses. Additionally, this amendment stipulated that the study would not be discontinued based upon the primary analysis of progression-free survival but rather the trial would continue until the primary analysis of the overall survival co-primary endpoint was completed.
23 July 2012	The main purpose of this amendment was to uncouple the interim analysis of progression-free survival from the completion of enrollment, which proceeded more quickly than expected. In addition, information on potential drug-drug interactions was updated based on completed clinical trials.
14 March 2013	<p>The main purpose of this amendment was to adjust the timing for the interim and final analyses of the co-primary endpoint of overall survival, based upon overall survival data from a similar population of chemotherapy-naïve metastatic castration-resistant prostate cancer patients. The final overall survival analysis was modified to occur after a minimum of 765 death events, and the formal interim analysis at approximately 516 death events.</p> <p>In addition, this amendment specified that independent central radiology review would continue until a minimum of 410 radiographic progression-free survival (rPFS) events occurred, and after that time scans only required local radiology review and confirmation.</p>
28 October 2013	The main purpose of this amendment was to follow the Independent Data Monitoring Committee (IDMC) recommendation to halt the double-blind period of the study due to compelling clinical benefit of MDV3100 (enzalutamide) over placebo. The pre-planned interim analysis of overall survival and the final analysis of radiographic progression-free survival (rPFS) for this study showed statistically significant improvement in both co-primary endpoints, rPFS (hazard ratio = 0.19, $p < 0.0001$) and overall survival (hazard ratio = 0.70, $p < 0.0001$). This protocol amendment allowed all ongoing enzalutamide-treated patients and ongoing and previous placebo-treated patients the opportunity to receive open-label enzalutamide and continue in this protocol.
29 April 2014	The main purpose of this amendment was to remove the requirement for assessment of skeletal-related events during open-label treatment with enzalutamide because adequate information was obtained for this endpoint during the double-blind period. Additionally, the on-study requirement for 12-lead electrocardiograms (ECGs) was removed because no safety signals had been detected to date through ECG monitoring of more than 2500 patients during clinical development.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported