



Clinical trial results:

AFFIRM: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy

Summary

EudraCT number	2009-013174-41
Trial protocol	BE GB FR ES DE AT IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	06 January 2017
First version publication date	06 January 2017

Trial information

Trial identification

Sponsor protocol code	CRPC2
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00974311
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medivation, Inc. Medivation is now a wholly owned subsidiary of Pfizer Inc.
Sponsor organisation address	525 Market St, San Francisco, United States, 94105
Public contact	Clinical Trial Disclosure, Medivation, Inc. , 1 415-543-3470, trialdisclosure@medivation.com
Scientific contact	Clinical Trial Disclosure, Medivation, Inc. , 1 415-543-3470, trialdisclosure@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	25 September 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2011
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 as compared to placebo as assessed by overall survival in patients with progressive castration-resistant prostate cancer whose disease was progressing after 1 or 2 prior chemotherapy regimens, at least 1 of which was docetaxel-based.

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 Council 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	22 September 2009
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	Netherlands: 46
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	United Kingdom: 132
Country: Number of subjects enrolled	Austria: 25
Country: Number of subjects enrolled	Belgium: 45
Country: Number of subjects enrolled	France: 273
Country: Number of subjects enrolled	Germany: 86
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	United States: 288
Country: Number of subjects enrolled	Chile: 11
Country: Number of subjects enrolled	Canada: 107
Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Australia: 93

Country: Number of subjects enrolled	South Africa: 6
Worldwide total number of subjects	1199
EEA total number of subjects	684

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)	362
From 65 to 84 years	819
85 years and over	18

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were randomized 2:1 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
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Arm title	Enzalutamide
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Arm description: -

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. Treatment continued until unacceptable toxicity, confirmed disease progression and the patient was scheduled to initiate a new systemic antineoplastic therapy, death, or withdrawal.

Arm title	Placebo
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Arm description: -

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 160 mg, administered as four 40-mg capsules, once per day by mouth. Treatment continued until unacceptable toxicity, confirmed disease progression and the patient was scheduled to initiate a new systemic antineoplastic therapy, death, or withdrawal.

Number of subjects in period 1	Enzalutamide	Placebo
Started	800	399
Completed	254	163
Not completed	546	236
Consent withdrawn by subject	9	5

Death	305	211
Continuing Treatment	231	19
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Enzalutamide
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Enzalutamide	Placebo	Total
Number of subjects	800	399	1199
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	232	130	362
>=65 years	568	269	837
Age continuous Units: years			
arithmetic mean	68.8	68.6	
standard deviation	± 7.96	± 8.39	-
Gender categorical Units: Subjects			
Male	800	399	1199

End points

End points reporting groups

Reporting group title	Enzalutamide
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Intent-to-treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who were randomized into the study.	
Subject analysis set title	Evaluable FACT-P
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All patients who were part of the ITT Population and had a global FACT-P score at baseline and at least 1 post-baseline assessment.	
Subject analysis set title	Evaluable Pain Palliation
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Patients with metastatic bone disease at baseline; provided answers to Question #3 of the Brief Pain Inventory – Short Form for a minimum of 4 out of 7 days in the baseline run-in period; stable baseline pain; stable analgesic use; and had an average pain score during the baseline run-in period of ≥ 4 .	

Primary: Overall Survival

End point title	Overall Survival
End point description: Overall survival is defined as time from randomization to death due to any cause. The duration of overall survival was right-censored for patients who were lost to follow-up since randomization or not known to have died at the data analysis cutoff date (this included patients who were known to have died after the data analysis cutoff date). '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	800	399		
Units: months				
median (confidence interval 95%)	18.4 (17.3 to 99999)	13.6 (11.3 to 15.8)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Enzalutamide v Placebo

Number of subjects included in analysis	1199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.75

Secondary: Radiographic Progression-free Survival

End point title	Radiographic Progression-free Survival
End point description:	
Radiographic progression-free survival was defined as time from randomization to the earliest objective evidence of radiographic progression or death due to any cause. Patients were assessed for objective disease progression at regularly scheduled visits. The consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) were taken into consideration for the determination of disease progression. Radiographic disease progression was defined by RECIST 1.1 for soft tissue disease, or the appearance of two or more new bone lesions on bone scan, as per the PCWG2 guidelines. Progression at the first scheduled reassessment at Week 13 required a confirmatory scan 6 or more weeks later. Patients who did not reach the endpoint were right censored at their last 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	800	399		
Units: months				
median (confidence interval 95%)	8.3 (8.2 to 9.4)	2.9 (2.8 to 3.4)		

Statistical analyses

Statistical analysis title	Radiographic Progression-free Survival
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.47

Secondary: Time to First Skeletal-related Event

End point title	Time to First Skeletal-related Event
End point description:	
The time to first skeletal-related event was defined as time from randomization to the occurrence of the first skeletal-related event. Patients were assessed for skeletal-related events at regularly scheduled visits. A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. Patients who did not reach the endpoint were right censored at their last assessment or for patients with no post-baseline assessment for skeletal-related event, at 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	800	399		
Units: months				
median (confidence interval 95%)	16.7 (14.6 to 19.1)	13.3 (9.9 to 99999)		

Statistical analyses

Statistical analysis title	Time to First Skeletal-Related Event
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.566
upper limit	0.835

Secondary: Response Rate for Functional Assessment of Cancer Therapy - Prostate (FACT-P)

End point title	Response Rate for Functional Assessment of Cancer Therapy - Prostate (FACT-P)
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End point description:

The FACT-P questionnaire is a 39-item questionnaire consisting of 5 domains; "physical well-being," "social/family well-being," "emotional well-being," "functional well-being," and "additional concerns" (consisting of items relating to prostate cancer and its treatment). Each item can be answered on a scale of 0–4. The sum of scores on all 5 domains constitutes the FACT-P.

Patients were defined as having a quality of life response if they had a 10-point improvement in their global FACT-P score, as compared with baseline, on two consecutive measurements obtained at least 3 weeks apart.

End point type	Secondary
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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	651	257		
Units: Percentage of patients				
number (confidence interval 95%)	43.2 (39.3 to 47.1)	18.3 (13.8 to 23.6)		

Statistical analyses

Statistical analysis title	Functional Assessment of Cancer Therapy - Prostate
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	908
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rate
Point estimate	24.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.8
upper limit	30.9

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

End point title	Time to Prostate-specific Antigen (PSA) Progression
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End point description:

Time to PSA progression was defined as time from randomization to PSA progression. Patients who did not reach the endpoint were right censored at their last assessment or for patients with no post-baseline

PSA assessment, date of randomization.

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, which was confirmed by a second consecutive value obtained 3 or more weeks later (required only if PSA progression did not occur at last PSA assessment). For patients with no PSA declines at Week 13, PSA progression date was defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline was documented, which was confirmed by a second consecutive value 3 or more weeks later (required only if PSA progression did not occur at last PSA assessment).

End point type	Secondary
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End point timeframe:

Baseline and at every study visit from week 13 while on study drug (up to 3 years)

End point values	Enzalutamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	800	399		
Units: months				
median (confidence interval 95%)	8.3 (5.8 to 8.3)	3 (2.9 to 3.7)		

Statistical analyses

Statistical analysis title	Time to PSA Progression
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1199
Analysis specification	Pre-specified
Analysis type	superiority
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.248
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.204
upper limit	0.303

Secondary: Percentage of Patients With Pain Palliation

End point title	Percentage of Patients With Pain Palliation
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End point description:

The proportion of patients with pain palliation was assessed for patients with a stable and sufficient pain burden at study entry. Pain burden was measured by question #3 of the Brief Pain Inventory (Short Form). This scale measures pain on a 0 to 10 scale with 0 indicating no pain and 10 indicating pain as bad as you can imagine. Pain palliation at Week 13 was determined for the proportion of men with baseline bone metastasis(es) who had baseline pain attributable to the metastasis(es). Palliation was defined as $\geq 30\%$ reduction in average pain score at Week 13 compared to baseline without a $\geq 30\%$ increase in analgesic use.

End point type	Secondary
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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	49	15		
Units: Percentage of Patients				
number (confidence interval 95%)	44.9 (30.7 to 59.8)	6.7 (0.2 to 31.9)		

Statistical analyses

Statistical analysis title	Percentage of Patients With Pain Palliation
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0079
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Rate of Pain Palliation
Point estimate	38.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.4
upper limit	57

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

End point title	Percentage of Patients With Prostate Specific Antigen (PSA) Response
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End point description:

Patients were evaluable for PSA response rate if they had a PSA level measured at baseline and at least 1 post-baseline assessment. PSA responses required confirmation with a subsequent assessment that was conducted at least 3 weeks later.

End point type	Secondary
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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	731	330		
Units: Percentage of Participants				
number (confidence interval 95%)				
PSA Decline >= 50% from baseline	54 (50.3 to 57.7)	1.5 (0.5 to 3.5)		
PSA Decline >= 90% from baseline	24.8 (21.7 to 28.1)	0.9 (0.2 to 2.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Soft-tissue Objective Response

End point title	Percentage of Patients With Soft-tissue Objective 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	446	208		
Units: Percentage of Patients				
number (confidence interval 95%)	28.9 (24.8 to 33.4)	3.8 (1.7 to 7.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of time after the first dose of study drug, and continuing up to 30 days after the patient's last dose of study drug, or prior to initiation of another systemic antineoplastic therapy, whichever occurred first.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Enzalutamide
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Enzalutamide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	268 / 800 (33.50%)	154 / 399 (38.60%)	
number of deaths (all causes)	308	212	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pain			
subjects affected / exposed	12 / 800 (1.50%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 16	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	8 / 800 (1.00%)	5 / 399 (1.25%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	4 / 800 (0.50%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to bone			

subjects affected / exposed	1 / 800 (0.13%)	5 / 399 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 800 (0.00%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute leukaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute monocytic leukaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bone marrow tumour cell infiltration			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm progression			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer stage unspecified			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 800 (0.38%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			

subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bladder catheter removal			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb operation			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain management			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract operation			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon polypectomy			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal dilation procedure			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurodesis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral stent insertion			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	17 / 800 (2.13%)	8 / 399 (2.01%)	
occurrences causally related to treatment / all	0 / 17	0 / 9	
deaths causally related to treatment / all	0 / 6	0 / 5	
Asthenia			
subjects affected / exposed	3 / 800 (0.38%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	5 / 800 (0.63%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	2 / 800 (0.25%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 800 (0.25%)	5 / 399 (1.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 800 (0.13%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 800 (0.25%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Euthanasia			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
General symptom			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (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 reaction			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 800 (0.38%)	4 / 399 (1.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pleural effusion			
subjects affected / exposed	2 / 800 (0.25%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 800 (0.38%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydropneumothorax			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 800 (0.25%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed mood			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Femur fracture			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (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			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (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			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation oesophagitis			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Adenomatous polyposis coli			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac failure			
subjects affected / exposed	2 / 800 (0.25%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular failure			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 800 (0.00%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	48 / 800 (6.00%)	15 / 399 (3.76%)	
occurrences causally related to treatment / all	0 / 50	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			

subjects affected / exposed	6 / 800 (0.75%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression			
subjects affected / exposed	1 / 800 (0.13%)	4 / 399 (1.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 800 (0.38%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 800 (0.38%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 800 (0.13%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Dizziness			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischemic attack			
subjects affected / exposed	3 / 800 (0.38%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Convulsion			

subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial neuropathy			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiduritis			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve compression			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	3 / 800 (0.38%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Akathisia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve palsies multiple			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial palsy			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lacunar infarction			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pachymeningitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglossal nerve paresis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual field defect			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 800 (2.63%)	12 / 399 (3.01%)	
occurrences causally related to treatment / all	1 / 28	2 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			
subjects affected / exposed	2 / 800 (0.25%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 800 (0.25%)	8 / 399 (2.01%)	
occurrences causally related to treatment / all	2 / 2	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	5 / 800 (0.63%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	2 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	5 / 800 (0.63%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 800 (0.25%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 800 (0.13%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 800 (0.38%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	3 / 800 (0.38%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 800 (0.00%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal mass			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (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			
Hyperhidrosis			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular purpura			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	12 / 800 (1.50%)	5 / 399 (1.25%)	
occurrences causally related to treatment / all	0 / 20	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	3 / 800 (0.38%)	8 / 399 (2.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	7 / 800 (0.88%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			
subjects affected / exposed	3 / 800 (0.38%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 800 (0.38%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 800 (0.25%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder obstruction			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral obstruction			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 800 (1.38%)	7 / 399 (1.75%)	
occurrences causally related to treatment / all	0 / 12	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	12 / 800 (1.50%)	4 / 399 (1.00%)	
occurrences causally related to treatment / all	0 / 12	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	12 / 800 (1.50%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	1 / 13	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	3 / 800 (0.38%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	3 / 800 (0.38%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	12 / 800 (1.50%)	5 / 399 (1.25%)	
occurrences causally related to treatment / all	1 / 12	0 / 5	
deaths causally related to treatment / all	1 / 2	0 / 1	
Urinary tract infection			
subjects affected / exposed	7 / 800 (0.88%)	5 / 399 (1.25%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	4 / 800 (0.50%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	3 / 800 (0.38%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 800 (0.13%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter bacteraemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall abscess			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infective exacerbation of chronic obstructive airways diseases			

subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			

subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pericarditis			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 800 (0.38%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 800 (0.25%)	3 / 399 (0.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 800 (0.13%)	2 / 399 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 800 (0.25%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia			

subjects affected / exposed	1 / 800 (0.13%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 800 (0.13%)	0 / 399 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	0 / 800 (0.00%)	1 / 399 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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	785 / 800 (98.13%)	390 / 399 (97.74%)	
Investigations			
Weight decreased			
subjects affected / exposed	94 / 800 (11.75%)	41 / 399 (10.28%)	
occurrences (all)	118	48	
Vascular disorders			
Hot flush			
subjects affected / exposed	162 / 800 (20.25%)	41 / 399 (10.28%)	
occurrences (all)	180	46	
Hypertension			
subjects affected / exposed	49 / 800 (6.13%)	11 / 399 (2.76%)	
occurrences (all)	60	12	
Nervous system disorders			
Headache			
subjects affected / exposed	93 / 800 (11.63%)	22 / 399 (5.51%)	
occurrences (all)	114	25	
Dizziness			
subjects affected / exposed	56 / 800 (7.00%)	22 / 399 (5.51%)	
occurrences (all)	62	21	
Paraesthesia			
subjects affected / exposed	52 / 800 (6.50%)	18 / 399 (4.51%)	
occurrences (all)	60	19	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	115 / 800 (14.38%)	76 / 399 (19.05%)	
occurrences (all)	183	112	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	269 / 800 (33.63%)	116 / 399 (29.07%)	
occurrences (all)	382	154	
Asthenia			
subjects affected / exposed	140 / 800 (17.50%)	67 / 399 (16.79%)	
occurrences (all)	197	92	
Oedema peripheral			

subjects affected / exposed	119 / 800 (14.88%)	52 / 399 (13.03%)	
occurrences (all)	141	61	
Pyrexia			
subjects affected / exposed	54 / 800 (6.75%)	23 / 399 (5.76%)	
occurrences (all)	62	31	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	265 / 800 (33.13%)	166 / 399 (41.60%)	
occurrences (all)	358	219	
Constipation			
subjects affected / exposed	188 / 800 (23.50%)	110 / 399 (27.57%)	
occurrences (all)	224	127	
Diarrhoea			
subjects affected / exposed	171 / 800 (21.38%)	70 / 399 (17.54%)	
occurrences (all)	231	81	
Vomiting			
subjects affected / exposed	130 / 800 (16.25%)	88 / 399 (22.06%)	
occurrences (all)	188	112	
Abdominal pain			
subjects affected / exposed	41 / 800 (5.13%)	23 / 399 (5.76%)	
occurrences (all)	44	23	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	79 / 800 (9.88%)	39 / 399 (9.77%)	
occurrences (all)	91	43	
Cough			
subjects affected / exposed	47 / 800 (5.88%)	25 / 399 (6.27%)	
occurrences (all)	48	27	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	69 / 800 (8.63%)	24 / 399 (6.02%)	
occurrences (all)	74	25	
Anxiety			
subjects affected / exposed	51 / 800 (6.38%)	16 / 399 (4.01%)	
occurrences (all)	57	16	
Depression			

subjects affected / exposed occurrences (all)	44 / 800 (5.50%) 44	18 / 399 (4.51%) 20	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	52 / 800 (6.50%) 63	18 / 399 (4.51%) 19	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	194 / 800 (24.25%) 270	95 / 399 (23.81%) 133	
Arthralgia subjects affected / exposed occurrences (all)	155 / 800 (19.38%) 213	71 / 399 (17.79%) 108	
Pain in extremity subjects affected / exposed occurrences (all)	120 / 800 (15.00%) 168	63 / 399 (15.79%) 93	
Bone pain subjects affected / exposed occurrences (all)	111 / 800 (13.88%) 145	68 / 399 (17.04%) 88	
Musculoskeletal pain subjects affected / exposed occurrences (all)	109 / 800 (13.63%) 133	40 / 399 (10.03%) 53	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	65 / 800 (8.13%) 80	34 / 399 (8.52%) 44	
Muscular weakness subjects affected / exposed occurrences (all)	68 / 800 (8.50%) 86	27 / 399 (6.77%) 33	
Myalgia subjects affected / exposed occurrences (all)	50 / 800 (6.25%) 53	26 / 399 (6.52%) 34	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	63 / 800 (7.88%) 78	28 / 399 (7.02%) 27	
Nasopharyngitis			

subjects affected / exposed occurrences (all)	41 / 800 (5.13%) 48	12 / 399 (3.01%) 17	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	200 / 800 (25.00%) 248	104 / 399 (26.07%) 126	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2009	The main purpose of this amendment was to decrease the dose of enzalutamide in this study based upon newly available data from a Phase 1-2 enzalutamide study.
01 April 2010	The main purpose of this amendment was to add the European Quality of Life 5-Domain Scale (EQ-5D), a standardized instrument for the measurement of health outcome. The EQ-5D data will be summarized descriptively by treatment group and study visit.
19 April 2011	The main purpose of this amendment was to adjust the target number of events required to conduct the final analysis of overall survival. The adjustment in the analysis plan was a result of the public release of data from a Phase 3 trial of abiraterone acetate (COU-AA-301 study) at the European Society of Medical Oncology annual meeting in October 2010. The data suggested that AFFIRM was over-powered, therefore this amendment reduced the target hazard ratio for the final overall survival analysis from 0.80 to 0.76 which reduced the target number of deaths from 786 to 650. Additional changes in this amendment included a simplification of the secondary endpoints. The progression-free survival endpoint was changed from a composite progression-free survival endpoint that included radiographic progression, skeletal-related events, and death to radiographic progression-free survival (radiographic progression and death only). Time to radiographic progression was removed however radiographic progression-free survival was retained.
05 January 2012	The main purpose of this amendment was to provide access to open-label enzalutamide to patients who were either actively taking enzalutamide at the time of unblinding or who were originally randomized to the placebo arm. This protocol amendment outlined the eligibility criteria as well as the study assessments for this open-label portion of the AFFIRM study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported