Clinical trial results:
PREVAIL: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve 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	14 February 2019

Results information

Result version number	v3 (current)
This version publication date	29 March 2020
First version publication date	18 July 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	C3431003 (MDV3100-03)

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the benefit of MDV3100 as compared to placebo as assessed by overall survival and by radiographic progression-free survival (rPFS).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 232
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Belgium: 57
Country: Number of subjects enrolled	Canada: 179
Country: Number of subjects enrolled	Denmark: 87
Country: Number of subjects enrolled	Finland: 33
Country: Number of subjects enrolled	France: 175
Country: Number of subjects enrolled	Germany: 83
Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Japan: 61
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	Slovakia: 27
Country: Number of subjects enrolled	Korea, Republic of: 78
Country: Number of subjects enrolled	Spain: 81
Country: Number of subjects enrolled	Sweden: 39

Country: Number of subjects enrolled	United Kingdom: 153
Country: Number of subjects enrolled	United States: 247
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:

Following the independent data monitoring committee's recommendation, a protocol amendment was implemented for double-blind phase to be proceeded to open-label phase, which allowed previously placebo treated subjects, who had not received commercial enzalutamide, the opportunity to receive open-label access to enzalutamide.

Period 1

Period 1 title	Double-blind
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:

Subjects 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	PF-04998299
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

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

Arm title	Placebo

Arm description:

Subjects 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, soft
Routes of administration	Oral use

Dosage and administration details:

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

Number of subjects in period 1	Enzalutamide	Placebo
Started	872	845
Safety population	871	844
Placebo Subjects CrossovertoEnzalutamide	0	234
Completed	0	234
Not completed	872	611
Adverse event, serious fatal	699	550
Consent withdrawn by subject	16	19
Unspecified	7	-
Lost to follow-up	8	4
Sponsor decision	142	38

Period 2

Period 2 title	Open-label
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Placebo Subjects Crossover to Enzalutamide

Arm description:

Subjects who received placebo in double-blind period and who agreed to proceed to open-label phase period, received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.

Arm type	Placebo Crossover to Experimental
Investigational medicinal product name	Placebo Crossover to Enzalutamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Subjects who received placebo in double-blind period and who agreed to proceed to open-label phase period, received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.

Number of subjects in period 2	Placebo Subjects Crossover to Enzalutamide
Started	234
Completed	0
Not completed	234
Adverse event, serious fatal	166
Consent withdrawn by subject	7

Unspecified	3
Lost to follow-up	5
Sponsor decision	53

Baseline characteristics

Reporting groups	
Reporting group title	Enzalutamide
Reporting group description:	
Subjects received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.	
Reporting group title	Placebo
Reporting group description:	
Subjects 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: Subjects			
<=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	-
Sex: Female, Male Units: Subjects			
Female	0	0	0
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:	
Subjects received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo, administered as four capsules, once per day by mouth.	
Reporting group title	Placebo Subjects Crossover to Enzalutamide
Reporting group description:	
Subjects who received placebo in double-blind period and who agreed to proceed to open-label phase period, received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.	

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 subjects who were alive at the time of the analysis data cutoff, overall survival was censored at the last date the subject was known to be alive or analysis data cutoff date, whichever was first. This included subjects who were known to have died after the data analysis cutoff date. Subjects with no post-baseline survival information were censored on the date of randomization. The upper limit of the 95% confidence interval was not calculable because an insufficient number of subjects reached the event at the final time point for assessment and has been denoted by '99999'. Intent to Treat (ITT) - All subjects randomly assigned to treatment.	
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	845		
Units: months				
median (confidence interval 95%)	32.4 (30.1 to 99999)	30.2 (28.0 to 99999)		

Statistical analyses

Statistical analysis title	Enzalutamide Versus (Vs.) Placebo
Comparison groups	Enzalutamide v Placebo

Number of subjects included in analysis	1717
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
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:

[1] - The hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with <1 favoring enzalutamide.
[2] - 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 (rPFS)

End point title	Radiographic Progression-free Survival (rPFS)

End point description:

rPFS:time from randomization to the first objective evidence of radiographic disease progression (RDP) assessed by 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; in soft tissue did not require a confirmatory scan for purposes of analysis. RDP was evaluated by independent central radiology review using RECIST 1.1 for soft tissue disease and PCWG2 guidelines for bone disease. ITT - All subjects randomly assigned to treatment excluding 84 subjects who were not randomized before the rPFS data cutoff date of 06 May 2012. The median time and its upper 95% confidence limit were not yet reached in the enzalutamide group because an insufficient number of subjects had an event at the time of analysis and has been denoted by '99999'.

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	801		
Units: months				
median (confidence interval 95%)	99999 (13.8 to 99999)	3.9 (3.7 to 5.4)		

Statistical analyses

Statistical analysis title	Enzalutamide Vs. Placebo

Statistical analysis description:

The hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.

Comparison groups	Enzalutamide v Placebo

Number of subjects included in analysis	1633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
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:

[3] - 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 (S-RE): time from randomization to date of the first occurrence of a S-RE for each subject. S-RE: 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. S-REs were recorded at each scheduled and unscheduled study visit and during long-term follow-up if a S-RE was not documented previously. Subjects who did not have a S-RE at the time of analysis data cutoff were censored at the date of last assessment indicating no evidence of S-RE. Subjects with no post baseline assessments were censored on the date of randomization. Upper limit of the 95% confidence interval was not calculable because insufficient number of subjects reached the event at the final time point for assessment, has been denoted by '99999'. ITT analysis set included all randomized subjects.

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	845		
Units: months				
median (confidence interval 95%)	31.1 (29.5 to 99999)	31.3 (23.9 to 99999)		

Statistical analyses

Statistical analysis title	Enzalutamide Vs. Placebo
Comparison groups	Enzalutamide v Placebo

Number of subjects included in analysis	1717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
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:

[4] - 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 is defined as the time from randomization to the date of initiation of cytotoxic chemotherapy for the treatment of prostate cancer for each subject. For subjects 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 subjects with no postbaseline assessments was censored on the date of randomization. The upper limit of the 95% confidence interval was not calculable because an insufficient number of subjects reached the event at the final time point for assessment, and has been denoted by '99999'. ITT analysis set included all randomized subjects.

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	845		
Units: months				
median (confidence interval 95%)	28.0 (25.8 to 99999)	10.8 (9.7 to 12.2)		

Statistical analyses

Statistical analysis title	Enzalutamide Vs. Placebo
Comparison groups	Enzalutamide v Placebo

Number of subjects included in analysis	1717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
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:

[5] - 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 subject. For subjects with PSA declines at week 13, the PSA progression date: date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir was documented, and confirmed 3 or more weeks later. For subjects with no PSA decline at week 13, the PSA progression date: date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above baseline was documented, and confirmed 3 or more weeks later. For subjects 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 subjects with no postbaseline assessments was censored on the date of randomization. ITT analysis set included all randomized subjects.

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	845		
Units: months				
median (confidence interval 95%)	11.2 (11.1 to 13.7)	2.8 (2.8 to 2.9)		

Statistical analyses

Statistical analysis title	Enzalutamide Vs. Placebo
Comparison groups	Enzalutamide v Placebo

Number of subjects included in analysis	1717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
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:

[6] - 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 Subjects With Prostate Specific Antigen (PSA) Response Greater Than or Equal to (>=) 50%

End point title	Percentage of Subjects With Prostate Specific Antigen (PSA) Response Greater Than or Equal to (>=) 50%

End point description:

PSA response was defined as a >= 50% reduction in PSA from baseline to the lowest post baseline PSA value and required confirmation by a consecutive assessment at least 3 weeks later. Subjects were evaluable for PSA response rate if a subject had a PSA level measured at baseline and at least one post baseline assessment. Evaluable ITT population - All subjects randomly assigned to treatment with PSA values at baseline and at least one post baseline 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	777		
Units: Percentage of subjects				
number (confidence interval 95%)	78 (75.1 to 80.7)	3.5 (2.3 to 5.0)		

Statistical analyses

Statistical analysis title	Enzalutamide Vs. Placebo
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	1631
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
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:

[7] - 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 is 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 subjects 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 subjects with measurable soft tissue disease at screening in each treatment group. ITT population With Measurable Disease - All subjects who were randomly assigned to treatment and had at least one target lesion at screening.

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	381		
Units: Percentage of subjects				
number (not applicable)	58.8	5.0		

Statistical analyses

Statistical analysis title	Enzalutamide Vs. Placebo
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	777
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
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:

[8] - 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.

Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to a maximum of 6.5 years that were absent before treatment or that worsened relative to pretreatment state. AEs included both serious and non-serious AEs. The safety analysis set included all randomized subjects who received at least 1 dose or partial dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline to discontinuation from the study or death, whichever occurred first (maximum duration of 6.5 years)

End point values	Enzalutamide	Placebo Subjects Crossover to Enzalutamide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	871	234	844	
Units: subjects				
AEs	857	212	791	
SAEs	384	104	229	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events (AEs) Greater Than or Equal to (>=) Grade 3, Based on National Cancer Institute Common Terminology Criteria for AEs (CTCAE), Version 4.0

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) Greater Than or Equal to (>=) Grade 3, Based on National Cancer Institute Common Terminology Criteria for AEs (CTCAE), Version 4.0

End point description:

An AE is any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. As per NCI CTCAE, Grade 3 events =medically significant but not immediately life-threatening, unacceptable or intolerable events, significantly interrupting usual daily activity, require systemic drug therapy/other treatment, Grade 4 events =subject to be in imminent danger of death. Grade 5 events =death. A treatment-emergent AE (TEAE) was defined as an AE that occurred from the date and time of the first dose of study drug up to a maximum duration of 6.5 years. Number of subjects with AEs of any of the Grade 3 or above (Grade 4, 5) were reported. The safety analysis set included all randomized subjects who received at least 1 dose or partial dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline to discontinuation from the study or death, whichever occurred first (maximum duration of 6.5 years)

End point values	Enzalutamide	Placebo Subjects Crossover to Enzalutamide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	871	234	844	
Units: subjects	465	129	318	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to a maximum duration of 6.5 years that were absent before treatment or that worsened relative to pre-treatment state. Relatedness to study drug was assessed by the investigator. The safety analysis set included all randomized subjects who received at least 1 dose or partial dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline to discontinuation from the study or death, whichever occurred first (maximum duration of 6.5 years)

End point values	Enzalutamide	Placebo Subjects Crossover to Enzalutamide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	871	234	844	
Units: subjects				
AEs|	579	119	423	
SAEs|	38	14	22	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to discontinuation from the study or death, whichever occurred first (maximum duration of 6.5 years)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event. Analysis was performed on safety set.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Enzalutamide

Reporting group description:

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

Reporting group title	Placebo Subjects Crossover to Enzalutamide

Reporting group description:

Subjects who received placebo in double-blind period and who agreed to proceed to open-label phase period, received enzalutamide 160 mg, administered as four 40-mg capsules, once per day by mouth.

Reporting group title	Placebo

Reporting group description:

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

Serious adverse events	Enzalutamide	Placebo Subjects Crossover to Enzalutamide	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	384 / 871 (44.09%)	104 / 234 (44.44%)	229 / 844 (27.13%)
number of deaths (all causes)	699	166	550
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pain			
subjects affected / exposed	18 / 871 (2.07%)	4 / 234 (1.71%)	17 / 844 (2.01%)
occurrences causally related to treatment / all	0 / 21	0 / 4	0 / 20
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	3 / 871 (0.34%)	2 / 234 (0.85%)	3 / 844 (0.36%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			

subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	4 / 871 (0.46%)	2 / 234 (0.85%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malignant pleural effusion			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to soft tissue			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to spine			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer metastatic			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Rectal cancer			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Tonsil cancer			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma gastric			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal cancer			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal adenocarcinoma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bladder			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone marrow			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to breast			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 871 (0.00%)	2 / 234 (0.85%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to peritoneum			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteosarcoma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer limited stage			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid adenoma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour embolism			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Tumour pain			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myeloid Leukaemia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal Cell Carcinoma			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain Neoplasm			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal Adenocarcinoma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal Cancer Metastatic			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Diffuse Large B-Cell Lymphoma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Cancer Recurrent			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal Cancer Metastatic			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Glioblastoma Multiforme			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases To Chest Wall			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases To Penis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic Neoplasm			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myxofibrosarcoma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's Lymphoma			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma Cell Myeloma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Small Cell Lung Cancer			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	4 / 871 (0.46%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 5	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	4 / 871 (0.46%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	2 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm rupture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Circulatory collapse			

subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian artery stenosis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aneurysm			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Stenosis			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cancer hormonal therapy			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain management			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee Arthroplasty			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radical Cystectomy			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical Hernia Repair			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	15 / 871 (1.72%)	6 / 234 (2.56%)	10 / 844 (1.18%)
occurrences causally related to treatment / all	0 / 15	0 / 6	0 / 10
deaths causally related to treatment / all	0 / 9	0 / 4	0 / 4
Disease progression			
subjects affected / exposed	10 / 871 (1.15%)	11 / 234 (4.70%)	7 / 844 (0.83%)
occurrences causally related to treatment / all	0 / 10	0 / 11	0 / 7
deaths causally related to treatment / all	0 / 10	0 / 11	0 / 6

Death			
subjects affected / exposed	5 / 871 (0.57%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 5	0 / 0	0 / 1
Oedema peripheral			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	3 / 844 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	5 / 871 (0.57%)	2 / 234 (0.85%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	2 / 871 (0.23%)	3 / 234 (1.28%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 871 (0.00%)	5 / 234 (2.14%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	2 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drowning			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Generalized oedema			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device complication			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Suprapubic pain			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adverse drug reaction			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Local swelling			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Malfunction			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical Device Pain			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-Organ Failure			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic obstruction			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular pain			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	6 / 871 (0.69%)	0 / 234 (0.00%)	7 / 844 (0.83%)
occurrences causally related to treatment / all	0 / 6	0 / 0	3 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 871 (0.57%)	0 / 234 (0.00%)	3 / 844 (0.36%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Epistaxis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrothorax			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising pneumonia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	3 / 871 (0.34%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Restrictive pulmonary disease			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal obstruction extrinsic			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 871 (0.23%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 871 (0.11%)	2 / 234 (0.85%)	4 / 844 (0.47%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriogram coronary			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulation time prolonged			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eastern cooperative oncology group performance status worsened			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalized ratio increased			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biopsy			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection Fraction Decreased			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram Abnormal			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	12 / 871 (1.38%)	2 / 234 (0.85%)	3 / 844 (0.36%)
occurrences causally related to treatment / all	2 / 12	2 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	7 / 871 (0.80%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	3 / 871 (0.34%)	1 / 234 (0.43%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	4 / 871 (0.46%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Humerus fracture			
subjects affected / exposed	4 / 871 (0.46%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	3 / 871 (0.34%)	1 / 234 (0.43%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 871 (0.00%)	2 / 234 (0.85%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Toxicity to various agents			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis radiation			

subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest injury			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural haematoma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis radiation			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation oesophagitis			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skeletal injury			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contrast media reaction			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematuria			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back Injury			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Vertebral Fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Injury			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Bile Leak			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Haematoma			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal Fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic Vertebral Fracture			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	10 / 871 (1.15%)	0 / 234 (0.00%)	6 / 844 (0.71%)
occurrences causally related to treatment / all	2 / 11	0 / 0	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	11 / 871 (1.26%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	3 / 12	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Atrioventricular block			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			

subjects affected / exposed	5 / 871 (0.57%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	3 / 871 (0.34%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive heart disease			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Flutter			
subjects affected / exposed	0 / 871 (0.00%)	2 / 234 (0.85%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Tachycardia			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block Complete			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Arrest			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Cardiac Failure			
subjects affected / exposed	5 / 871 (0.57%)	3 / 234 (1.28%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	2 / 6	0 / 3	0 / 2
deaths causally related to treatment / all	1 / 4	0 / 2	0 / 0
Cardiac Failure Congestive			

subjects affected / exposed	2 / 871 (0.23%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	3 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Cardiopulmonary Failure			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiovascular Insufficiency			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary Artery Disease			
subjects affected / exposed	6 / 871 (0.69%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Stenosis			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Cardiomyopathy			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Ventricular Failure			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral Valve Disease			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral Valve Incompetence			

subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	6 / 871 (0.69%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 6	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular Tachycardia			
subjects affected / exposed	2 / 871 (0.23%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid Valve Incompetence			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Fibrillation			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Wolff-Parkinson-White Syndrome			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	35 / 871 (4.02%)	10 / 234 (4.27%)	25 / 844 (2.96%)
occurrences causally related to treatment / all	0 / 37	0 / 10	0 / 25
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	8 / 871 (0.92%)	3 / 234 (1.28%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 8	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	7 / 871 (0.80%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	1 / 7	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cauda equina syndrome			
subjects affected / exposed	4 / 871 (0.46%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	6 / 871 (0.69%)	0 / 234 (0.00%)	3 / 844 (0.36%)
occurrences causally related to treatment / all	1 / 6	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain injury			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral haemorrhage			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicobrachial syndrome			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma hepatic			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dementia			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningorrhagia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Reversible ischaemic neurological deficit			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord ischaemia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vith nerve disorder			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complex partial seizures			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Cord Compression			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cranial Nerve Paralysis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand Mal Convulsion			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage Intracranial			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxic-Ischaemic Encephalopathy			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss Of Consciousness			

subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological Symptom			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory Loss			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vith Nerve Paralysis			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiduritis			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoplegia			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Status Epilepticus			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	18 / 871 (2.07%)	6 / 234 (2.56%)	9 / 844 (1.07%)
occurrences causally related to treatment / all	1 / 23	1 / 10	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic Uraemic Syndrome			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic Thrombocytopenic Purpura			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet Dysfunction			

subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amaurosis			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery occlusion			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid Ptosis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal Vein Occlusion			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 871 (0.57%)	2 / 234 (0.85%)	5 / 844 (0.59%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 871 (0.34%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	2 / 3	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 871 (0.34%)	2 / 234 (0.85%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 871 (0.46%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Melaena			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	2 / 871 (0.23%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal haemorrhage			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal stenosis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Stenosis			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Ulcer			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal Spasm			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic Ulcer			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Haemorrhage			
subjects affected / exposed	0 / 871 (0.00%)	2 / 234 (0.85%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile Duct Stone			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Cyst			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Toxic skin eruption			

subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swelling face			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash Maculo-Papular			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	10 / 871 (1.15%)	3 / 234 (1.28%)	13 / 844 (1.54%)
occurrences causally related to treatment / all	0 / 13	0 / 4	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	11 / 871 (1.26%)	3 / 234 (1.28%)	12 / 844 (1.42%)
occurrences causally related to treatment / all	0 / 16	0 / 5	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	8 / 871 (0.92%)	1 / 234 (0.43%)	9 / 844 (1.07%)
occurrences causally related to treatment / all	0 / 10	0 / 1	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	2 / 871 (0.23%)	1 / 234 (0.43%)	11 / 844 (1.30%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal failure acute			

subjects affected / exposed	6 / 871 (0.69%)	2 / 234 (0.85%)	5 / 844 (0.59%)
occurrences causally related to treatment / all	3 / 6	0 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Ureteric obstruction			
subjects affected / exposed	4 / 871 (0.46%)	1 / 234 (0.43%)	4 / 844 (0.47%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive uropathy			
subjects affected / exposed	5 / 871 (0.57%)	3 / 234 (1.28%)	6 / 844 (0.71%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bladder outlet obstruction			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	3 / 844 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postrenal failure			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	3 / 844 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary bladder haemorrhage			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute prerenal failure			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder obstruction			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure chronic			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral meatus stenosis			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral obstruction			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine flow decreased			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neck obstruction			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Micturition urgency			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Ureteric			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral Stenosis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Incontinence			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic Syndrome			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Urinary			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Goitre			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pathological Fracture			
subjects affected / exposed	15 / 871 (1.72%)	3 / 234 (1.28%)	6 / 844 (0.71%)
occurrences causally related to treatment / all	0 / 16	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	4 / 871 (0.46%)	0 / 234 (0.00%)	5 / 844 (0.59%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	5 / 844 (0.59%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	8 / 871 (0.92%)	2 / 234 (0.85%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 8	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	4 / 871 (0.46%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			

subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	3 / 844 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	2 / 871 (0.23%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteolysis			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periostitis			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			

subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Spinal Stenosis			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial Cyst			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	14 / 871 (1.61%)	8 / 234 (3.42%)	7 / 844 (0.83%)
occurrences causally related to treatment / all	0 / 19	0 / 9	0 / 7
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 0
Urinary tract infection			
subjects affected / exposed	8 / 871 (0.92%)	10 / 234 (4.27%)	5 / 844 (0.59%)
occurrences causally related to treatment / all	0 / 13	0 / 10	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	5 / 871 (0.57%)	4 / 234 (1.71%)	3 / 844 (0.36%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	3 / 871 (0.34%)	1 / 234 (0.43%)	4 / 844 (0.47%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	4 / 871 (0.46%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			

subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder abscess			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis staphylococcal			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 871 (0.11%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection fungal			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Sinusitis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis Bacterial			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Infective			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Sepsis			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Urinary Tract Infection			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected Dermal Cyst			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 871 (0.23%)	3 / 234 (1.28%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Meningitis Pneumococcal			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative Wound Infection			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Sepsis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			

subjects affected / exposed	0 / 871 (0.00%)	2 / 234 (0.85%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 871 (0.23%)	1 / 234 (0.43%)	3 / 844 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	2 / 871 (0.23%)	1 / 234 (0.43%)	2 / 844 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	3 / 871 (0.34%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Fluid retention			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	2 / 871 (0.23%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 871 (0.00%)	0 / 234 (0.00%)	1 / 844 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	0 / 871 (0.00%)	1 / 234 (0.43%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 871 (0.11%)	0 / 234 (0.00%)	0 / 844 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Enzalutamide	Placebo Subjects Crossover to Enzalutamide	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	814 / 871 (93.46%)	180 / 234 (76.92%)	723 / 844 (85.66%)
Vascular disorders			
Hot flush			
subjects affected / exposed	159 / 871 (18.25%)	11 / 234 (4.70%)	66 / 844 (7.82%)
occurrences (all)	169	13	67

Hypertension			
subjects affected / exposed	148 / 871 (16.99%)	28 / 234 (11.97%)	36 / 844 (4.27%)
occurrences (all)	210	30	42
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	332 / 871 (38.12%)	63 / 234 (26.92%)	220 / 844 (26.07%)
occurrences (all)	458	76	264
Asthenia			
subjects affected / exposed	122 / 871 (14.01%)	15 / 234 (6.41%)	69 / 844 (8.18%)
occurrences (all)	219	27	78
Oedema peripheral			
subjects affected / exposed	115 / 871 (13.20%)	20 / 234 (8.55%)	70 / 844 (8.29%)
occurrences (all)	143	25	83
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	95 / 871 (10.91%)	2 / 234 (0.85%)	58 / 844 (6.87%)
occurrences (all)	109	2	62
Dyspnoea			
subjects affected / exposed	88 / 871 (10.10%)	14 / 234 (5.98%)	60 / 844 (7.11%)
occurrences (all)	105	15	66
Psychiatric disorders			
Insomnia			
subjects affected / exposed	78 / 871 (8.96%)	10 / 234 (4.27%)	48 / 844 (5.69%)
occurrences (all)	86	10	48
Investigations			
Weight decreased			
subjects affected / exposed	122 / 871 (14.01%)	26 / 234 (11.11%)	72 / 844 (8.53%)
occurrences (all)	148	34	85
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	136 / 871 (15.61%)	15 / 234 (6.41%)	42 / 844 (4.98%)
occurrences (all)	191	17	45
Nervous system disorders			
Headache			
subjects affected / exposed	102 / 871 (11.71%)	15 / 234 (6.41%)	59 / 844 (6.99%)
occurrences (all)	139	23	70

Dizziness			
subjects affected / exposed	85 / 871 (9.76%)	13 / 234 (5.56%)	54 / 844 (6.40%)
occurrences (all)	104	16	60
Dysgeusia			
subjects affected / exposed	67 / 871 (7.69%)	5 / 234 (2.14%)	31 / 844 (3.67%)
occurrences (all)	73	6	31
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	76 / 871 (8.73%)	23 / 234 (9.83%)	68 / 844 (8.06%)
occurrences (all)	109	52	106
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	211 / 871 (24.23%)	34 / 234 (14.53%)	192 / 844 (22.75%)
occurrences (all)	271	38	219
Constipation			
subjects affected / exposed	220 / 871 (25.26%)	38 / 234 (16.24%)	145 / 844 (17.18%)
occurrences (all)	262	42	166
Diarrhoea			
subjects affected / exposed	160 / 871 (18.37%)	20 / 234 (8.55%)	121 / 844 (14.34%)
occurrences (all)	219	25	156
Vomiting			
subjects affected / exposed	64 / 871 (7.35%)	9 / 234 (3.85%)	70 / 844 (8.29%)
occurrences (all)	77	10	91
Abdominal pain			
subjects affected / exposed	56 / 871 (6.43%)	4 / 234 (1.71%)	31 / 844 (3.67%)
occurrences (all)	62	7	45
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	31 / 871 (3.56%)	14 / 234 (5.98%)	21 / 844 (2.49%)
occurrences (all)	36	16	22
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	93 / 871 (10.68%)	11 / 234 (4.70%)	43 / 844 (5.09%)
occurrences (all)	139	13	53
Pollakiuria			
subjects affected / exposed	62 / 871 (7.12%)	6 / 234 (2.56%)	37 / 844 (4.38%)
occurrences (all)	80	7	40

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	280 / 871 (32.15%)	32 / 234 (13.68%)	188 / 844 (22.27%)
occurrences (all)	415	39	271
Arthralgia			
subjects affected / exposed	206 / 871 (23.65%)	22 / 234 (9.40%)	137 / 844 (16.23%)
occurrences (all)	322	25	193
Pain in extremity			
subjects affected / exposed	124 / 871 (14.24%)	13 / 234 (5.56%)	97 / 844 (11.49%)
occurrences (all)	173	17	124
Bone pain			
subjects affected / exposed	100 / 871 (11.48%)	18 / 234 (7.69%)	116 / 844 (13.74%)
occurrences (all)	127	20	142
Musculoskeletal pain			
subjects affected / exposed	112 / 871 (12.86%)	28 / 234 (11.97%)	74 / 844 (8.77%)
occurrences (all)	142	37	90
Musculoskeletal chest pain			
subjects affected / exposed	73 / 871 (8.38%)	5 / 234 (2.14%)	40 / 844 (4.74%)
occurrences (all)	85	5	50
Myalgia			
subjects affected / exposed	59 / 871 (6.77%)	8 / 234 (3.42%)	49 / 844 (5.81%)
occurrences (all)	72	8	60
Muscular Weakness			
subjects affected / exposed	45 / 871 (5.17%)	8 / 234 (3.42%)	27 / 844 (3.20%)
occurrences (all)	58	9	33
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	70 / 871 (8.04%)	11 / 234 (4.70%)	56 / 844 (6.64%)
occurrences (all)	94	13	68
Nasopharyngitis			
subjects affected / exposed	74 / 871 (8.50%)	6 / 234 (2.56%)	44 / 844 (5.21%)
occurrences (all)	94	12	48
Upper respiratory tract infection			
subjects affected / exposed	61 / 871 (7.00%)	7 / 234 (2.99%)	30 / 844 (3.55%)
occurrences (all)	79	8	38
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	182 / 871 (20.90%) 225	36 / 234 (15.38%) 48	139 / 844 (16.47%) 166

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2012	Interim analysis of progression-free survival was uncoupled from the completion of enrollment, which proceeded more quickly than expected.
28 October 2013	Access to MDV3100 (enzalutamide) to subjects in PREVAIL who may have been derived of clinical benefit. Subjects receiving enzalutamide or placebo as randomized double-blind treatment may receive enzalutamide during the open-label period.
29 April 2014	Removed 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 were detected to date through ECG monitoring.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported