Clinical trial results:
A Multicenter, Single-arm, Open-label, Postmarketing Safety Study to Evaluate the Risk of Seizure Among Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated with Enzalutamide Who Are at Potential Increased Risk of Seizure (UPWARD)

Summary

EudraCT number	2013-003022-92
Trial protocol	SE DE HU GB BE FI IT CZ GR ES
Global end of trial date	11 January 2019

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	9785-CL-0403

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01977651
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc.
Sponsor organisation address	1 Astellas Way, Northbrook, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., 800 888-7704, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., 800 888-7704, astellas.resultsdisclosure@astellas.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	11 January 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the seizure rate and monitor the safety of enzalutamide treatment in participants with metastatic castration-resistant prostate cancer (mCRPC) known to have risk factor(s) for seizure.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 September 2013
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	Canada: 5
Country: Number of subjects enrolled	Chile: 57
Country: Number of subjects enrolled	Czech Republic: 17
Country: Number of subjects enrolled	Finland: 23
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Israel: 61
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 76
Country: Number of subjects enrolled	Argentina: 36
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Belgium: 6

Worldwide total number of subjects	424
EEA total number of subjects	149

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)	66
From 65 to 84 years	313
85 years and over	45

Subject disposition

Recruitment

Recruitment details:

Study enrolled male participants with histologically-confirmed metastatic adenocarcinoma of prostate with ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) analogue (agonist or antagonist) or a prior orchiectomy. Participants were evaluated by a neurologist who determined they had at least 1 risk factor for seizure.

Pre-assignment

Screening details:

Participants who met all inclusion and none of the exclusion criteria were enrolled into the study, completing a 4-month treatment period. At the end of treatment period participants who benefited from the treatment were allowed to continue in the extension period for 12 months.

Pre-assignment period milestones

Number of subjects started	424
Number of subjects completed	423

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Participant enrolled but died before treatment: 1

Period 1

Period 1 title	Treatment Period 1 (Primary 4 Months)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Enzalutamide 160 mg

Arm description:

Participants received 160 mg of enzalutamide orally once a day, for 4 months.

Arm type	Experimental
Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	MDV3100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 4 capsules (40 mg each) of enzalutamide orally once a day, for a total daily dose of 160 mg. Treatment was given with or without food and as close as possible to the same time each day.

Number of subjects in period 1[1]	Enzalutamide 160 mg
Started	423
Received treatment	423
Completed	322
Not completed	101

Progressive disease	43
Death	3
Physician decision	4
Adverse event, non-fatal	34
Consent withdrawn by subject	17

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One participant was screened and enrolled but died the following day before receiving the study drug.

Period 2

Period 2 title	Treatment Period 2 (Extension 12 Months)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Enzalutamide 160 mg

Arm description:

At the end of the 4-month treatment period, participants who were assessed as deriving benefit from enzalutamide treatment continued in the 12 month extension period. The total study drug treatment duration for the extended period depended on individual clinical benefit. If a participant experienced a Grade 3 or higher toxicity that was attributed to enzalutamide and could not be ameliorated by the use of adequate medical intervention, treatment with enzalutamide was allowed to be interrupted for 1 week or until the toxicity grade improved to Grade 2 or lower severity. Subsequently, enzalutamide was restarted at the original dose 160 mg per day or a reduced dose 120 or 80 mg per day in consultation with the medical monitor.

Arm type	Experimental
Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	MDV3100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 4 capsules (40 mg each) of enzalutamide orally once a day, for a total daily dose of 160 mg. Treatment was given with or without food and as close as possible to the same time each day.

Number of subjects in period 2[2]	Enzalutamide 160 mg
Started	287
Completed	157
Not completed	130
Progressive disease	86
Death	10
Miscellaneous	1
Physician decision	6
Adverse event, non-fatal	14

Consent withdrawn by subject	11
Lost to follow-up	2

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only participants who were assessed to benefit from enzalutamide treatment were treated in the extension period after completing the 4-month treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Enzalutamide 160 mg
Reporting group description:	
Participants received 160 mg of enzalutamide orally once a day, for 4 months.	

Reporting group values	Enzalutamide 160 mg	Total	
Number of subjects	423	423	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	73.2		
standard deviation	± 8.99	-	
Gender categorical Units:			
Male	423	423	
Race			
The analysis population was the safety analysis set (SAF), which consisted of participants who received at least 1 dose of study drug and for whom any data was reported after first dose of study drug.			
Units: Subjects			
White	381	381	
Black or African American	9	9	
Asian	25	25	
American Indian or Alaskan Native	0	0	
Native Hawaiian or other Pacific Islander	1	1	
Other	4	4	
No data	3	3	
Ethnicity			
The analysis population was the safety analysis set (SAF).			
Units: Subjects			
Hispanic or Latino	89	89	
Not Hispanic or Latino	331	331	
No data	3	3	
Eastern Cooperative Oncology Group (ECOG) At Study Entry			
ECOG performance status is a scale used to measure disease progression and impact on daily activities. Scores range from 0 to 5, with 0- signifying fully active participant, grade 1-restricted in physically strenuous activity; grade 2 - ambulatory and capable of all self-care, unable to work; grade 3- capable of only limited self-care, confined to bed more than 50% of waking hours; grade 4-completely disabled and grade 5- dead. Negative change scores indicate an improvement and positive scores indicate a decline in participant's disease progression and their daily activities. (SAF)			
Units: Subjects			
Score 0	188	188	
Score 1	190	190	
Score 2	45	45	

End points

End points reporting groups

Reporting group title	Enzalutamide 160 mg

Reporting group description:

Participants received 160 mg of enzalutamide orally once a day, for 4 months.

Reporting group title	Enzalutamide 160 mg

Reporting group description:

At the end of the 4-month treatment period, participants who were assessed as deriving benefit from enzalutamide treatment continued in the 12 month extension period. The total study drug treatment duration for the extended period depended on individual clinical benefit. If a participant experienced a Grade 3 or higher toxicity that was attributed to enzalutamide and could not be ameliorated by the use of adequate medical intervention, treatment with enzalutamide was allowed to be interrupted for 1 week or until the toxicity grade improved to Grade 2 or lower severity. Subsequently, enzalutamide was restarted at the original dose 160 mg per day or a reduced dose 120 or 80 mg per day in consultation with the medical monitor.

Primary: The Percentage of Evaluable Participants With at Least One Confirmed Seizure as Adjudicated by the Independent Adjudication Committee (IAC)

End point title	The Percentage of Evaluable Participants With at Least One Confirmed Seizure as Adjudicated by the Independent Adjudication Committee (IAC)[1]

End point description:

The analysis population was the seizure risk evaluation set (SRES), which consisted of of all evaluable participants. An evaluable participant was defined as a participant with a confirmed seizure during the 4-month treatment period of the study or a participant who completed at least 3 months (75%) of the planned treatment. One participant had their first confirmed seizure event as adjudicated by the IAC on Day 147, post 4 months of treatment. The subject's total duration of exposure is 79 days, which included a long interruption of study drug from Day 21 to Day 88. This subject is included in SRES but the IAC confirmed first seizure event was not included in the primary analysis.

End point type	Primary

End point timeframe:

Day 1 up to Week 17 (End of Treatment)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There were no pre-specified statistical analyses planned for this end point.

End point values	Enzalutamide 160 mg			
Subject group type	Reporting group			
Number of subjects analysed	366			
Units: Percentage of participants				
number (confidence interval 95%)	1.1 (0.3 to 2.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug up to 30 days after last dose of study drug (up to 12 months)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16

Reporting groups	
Reporting group title	Enzalutamide 160 mg
Reporting group description:	
Participants received 160 mg of enzalutamide orally once a day, for 4 months.	

Serious adverse events	Enzalutamide 160 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	193 / 423 (45.63%)		
number of deaths (all causes)	62		
number of deaths resulting from adverse events	58		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Bladder lesion excision			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Internal fixation of fracture			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint arthroplasty			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Benign neoplasm of ureter			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangiocarcinoma			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	34 / 423 (8.04%)		
occurrences causally related to treatment / all	1 / 39		
deaths causally related to treatment / all	1 / 23		

Metastases to liver				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastases to lymph nodes				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to spine				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neoplasm malignant				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal cancer				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin cancer				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Asthenia				
subjects affected / exposed	3 / 423 (0.71%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Device leakage				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Drug ineffective				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	3 / 423 (0.71%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	10 / 423 (2.36%)			
occurrences causally related to treatment / all	4 / 18			
deaths causally related to treatment / all	1 / 5			
Glassy eyes				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
subjects affected / exposed	1 / 423 (0.24%)			

occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pain				
subjects affected / exposed	5 / 423 (1.18%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Performance status decreased				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	8 / 423 (1.89%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden cardiac death				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Psychiatric disorders				
Agitation				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	10 / 423 (2.36%)			
occurrences causally related to treatment / all	5 / 10			
deaths causally related to treatment / all	0 / 0			
Delirium				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to	1 / 2			

treatment / all				
deaths causally related to treatment / all	0 / 0			
Disorientation				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fear of falling				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paranoia				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Panic attack				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Pelvic pain				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				

subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	10 / 423 (2.36%)		
occurrences causally related to treatment / all	1 / 10		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	4 / 423 (0.95%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 423 (0.24%)		

occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Subdural haemorrhage				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urostomy complication				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystoscopy				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to	0 / 2			

treatment / all				
deaths causally related to treatment / all	0 / 0			
Prostatic specific antigen increased				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Angina pectoris				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	4 / 423 (0.95%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atrioventricular block complete				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			

deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	4 / 423 (0.95%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 1			
Cardiac failure chronic				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiac failure congestive				
subjects affected / exposed	3 / 423 (0.71%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 2			
Cardiogenic shock				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Coronary artery disease				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mitral valve incompetence				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	5 / 423 (1.18%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 3			
Right ventricular failure				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Ventricular tachycardia				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	5 / 423 (1.18%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orthopnoea				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	3 / 423 (0.71%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Pulmonary embolism				
subjects affected / exposed	4 / 423 (0.95%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 1			
Pulmonary congestion				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory arrest				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary oedema				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory disorder				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	9 / 423 (2.13%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Aplastic anaemia				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Anaemia of malignant disease				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				

subjects affected / exposed	3 / 423 (0.71%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Altered state of consciousness				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid artery stenosis				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Brain stem stroke				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Central nervous system haemorrhage				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral artery occlusion				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral artery stenosis				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				

subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 1		
Cerebral infarction			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	8 / 423 (1.89%)		
occurrences causally related to treatment / all	4 / 10		
deaths causally related to treatment / all	0 / 0		
Diplegia			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysgeusia			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 423 (0.24%)		

occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic stroke			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
IIIrd nerve paralysis			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Nerve root compression			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Parkinson's disease			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		

deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	7 / 423 (1.65%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 1			
Syncope				
subjects affected / exposed	5 / 423 (1.18%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Transient global amnesia				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	4 / 423 (0.95%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Blindness				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye pain				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			

deaths causally related to treatment / all	0 / 0		
Vision blurred			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertigo			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 423 (1.42%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Colonic obstruction			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	3 / 423 (0.71%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		

deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Nausea			
subjects affected / exposed	4 / 423 (0.95%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Proctalgia			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	7 / 423 (1.65%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Anuria			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	2 / 2		

deaths causally related to treatment / all	1 / 1			
Bladder dilatation				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysuria				
subjects affected / exposed	4 / 423 (0.95%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	8 / 423 (1.89%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 0			
Nephritic syndrome				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	4 / 423 (0.95%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Urethral stenosis				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	4 / 423 (0.95%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			

Urinary bladder haemorrhage				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	5 / 423 (1.18%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatocellular injury				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Jaundice cholestatic				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	6 / 423 (1.42%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	8 / 423 (1.89%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 0			
Flank pain				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Lumbar spinal stenosis				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	3 / 423 (0.71%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	3 / 423 (0.71%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	3 / 423 (0.71%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pubic pain				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				

Decreased appetite			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cachexia			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	5 / 423 (1.18%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Failure to thrive			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	4 / 423 (0.95%)		

occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Hypophagia				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anal abscess				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Candiduria				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to	0 / 1			

treatment / all				
deaths causally related to treatment / all	0 / 0			
Corona virus infection				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Erysipelas				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			

deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	13 / 423 (3.07%)			
occurrences causally related to treatment / all	0 / 16			
deaths causally related to treatment / all	0 / 3			
Pyelonephritis				
subjects affected / exposed	2 / 423 (0.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	3 / 423 (0.71%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	4 / 423 (0.95%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Spinal cord infection				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal urinary tract infection				
subjects affected / exposed	1 / 423 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Tracheobronchitis			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	4 / 423 (0.95%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial			
subjects affected / exposed	3 / 423 (0.71%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 423 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection staphylococcal			
subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	2 / 423 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Enzalutamide 160 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	318 / 423 (75.18%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	24 / 423 (5.67%)		
occurrences (all)	26		

Hypertension			
subjects affected / exposed	31 / 423 (7.33%)		
occurrences (all)	36		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	24 / 423 (5.67%)		
occurrences (all)	31		
Investigations			
Weight decreased			
subjects affected / exposed	26 / 423 (6.15%)		
occurrences (all)	27		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	33 / 423 (7.80%)		
occurrences (all)	37		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	53 / 423 (12.53%)		
occurrences (all)	82		
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 423 (5.91%)		
occurrences (all)	26		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	86 / 423 (20.33%)		
occurrences (all)	113		
Oedema peripheral			
subjects affected / exposed	33 / 423 (7.80%)		
occurrences (all)	39		
Fatigue			
subjects affected / exposed	92 / 423 (21.75%)		
occurrences (all)	120		
Pain			
subjects affected / exposed	23 / 423 (5.44%)		
occurrences (all)	28		

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 27 / 423 (6.38%) 34		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 46 / 423 (10.87%) 50 43 / 423 (10.17%) 54 55 / 423 (13.00%) 65 24 / 423 (5.67%) 29		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 47 / 423 (11.11%) 56 68 / 423 (16.08%) 82 22 / 423 (5.20%) 24 27 / 423 (6.38%) 33		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 77 / 423 (18.20%) 92		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2013	The changes include: Updates were made to fulfill requirements for a Post Authorization Safety Study as defined by EMA: o The sample size calculation was refined to include the incidence rate of seizure (2.8 per 100 person-years). o The description of the study design was expanded to include potential limitations of the study design, data sources and analytical methods. o A statement on the source population was added to state that the patients were drawn from various sources including hospitals, private practices and community-based organizations. o The expected age range of the patient population was added. o A statement was added that patients with alcoholism were allowed into the study assuming eligibility criteria were met. o An appendix outlining the countries planned for participation in the study was added. o An appendix outlining the study milestones was added. ● The suspected seizure event visit window was updated to accommodate logistical challenges that could arise due to hospitalization of patients or transportation challenges in rural areas where modes of transportation could be limited. ● The anti-seizure drug pregabalin was re-categorized as an acceptable drug unlikely to cause interaction with enzalutamide after the team re-examined the potential for drug-drug interaction with pregabalin and enzalutamide. The re-categorization was based on the determination that pregabalin undergoes very little metabolism, is excreted in the urine mostly intact as parent and does not inhibit or induce metabolic enzymes in vitro. ● The timing of additional radiographic disease assessments was clarified to ensure a frequency of no more than every 12 weeks to avoid over-exposure to a patient. ● A statement on data interpretation of enzalutamide was added to clarify that no direct comparison was planned but that the results from the study would be interpreted in the context of all available relevant data.
25 November 2013	The changes include: The word “Adverse Events” was deleted from the list of data to be collected for screen failures based on the timing of AE collection defined in the protocol. ● Additional nonsubstantial changes were made to add EudraCT information, update contact information and incorporate minor wording changes.

20 August 2014	The changes include: The seizure incidence rate was changed from "0.5% to 0.9%" to "< 1%" and "cognitive/memory impairment" was changed from a potential risk to an identified risk. The changes were based on more current experience regarding enzalutamide and seizures as reflected in the updated Investigator's Brochure. ● Additional nonsubstantial changes were made including an increase in the number of sites participating in the study, addition of a statement outlining the limit of patients enrolled under a specific risk category (i.e., class of medication) to ensure patients with a reasonably balanced set of risk characteristics were enrolled in the study, addition of a statement to allow for destruction of the study drug at the site with the sponsor permission, addition of a statement indicating patients with Alzheimer's disease are permitted to be enrolled into the study and the incorporation of other minor wording changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

After completing 12 months extension period participants who were assessed to benefit from enzalutamide completed their treatment in another Astellas study.

Notes: