Clinical trial results:
A Randomized, Double-Blind, Phase II, Efficacy and Safety Study of MDV3100 (ASP9785) vs. Bicalutamide in Castrate Men with Metastatic Prostate Cancer

Summary

EudraCT number	2010-021868-15
Trial protocol	GB BE DE DK
Global end of trial date	08 November 2017

Results information

Result version number	v2 (current)
This version publication date	30 August 2019
First version publication date	17 November 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	9785-CL-0222

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01288911
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc. (APGD)
Sponsor organisation address	1 Astellas Way, Northbrook, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), 800 888-7704, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), 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	16 February 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 November 2017
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 determine the progression-free survival (PFS) of enzalutamide as compared to bicalutamide. All participants that entered the open-label period of the study received enzalutamide, including those that received biculatamide in the double-blind period.

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	22 March 2011
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	Belgium: 26
Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	Denmark: 22
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	United Kingdom: 86
Country: Number of subjects enrolled	United States: 115
Worldwide total number of subjects	375
EEA total number of subjects	221

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	92
From 65 to 84 years	260
85 years and over	23

Subject disposition

Recruitment

Recruitment details:

Men with metastatic castration-resistant prostate cancer (mCRPC) were enrolled at 84 sites in a total of 8 countries.

Pre-assignment

Screening details:

Participants were stratified by whether bilateral orchiectomy or receipt of luteinizing hormone-releasing hormone (LHRH) agonist/antagonist therapy started before or after the diagnosis of metastases and by site.

Period 1

Period 1 title	Double-blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Enzalutamide

Arm description:

Participants received enzalutamide 160 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.

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

Dosage and administration details:

Participants received enzalutamide 160 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.

Arm title	Bicalutamide

Arm description:

Participants received bicalutamide 50 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.

Arm type	Active comparator
Investigational medicinal product name	Bicalutamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received bicalutamide 50 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.

Number of subjects in period 1	Enzalutamide	Bicalutamide
Started	184	191
Received Treatment	183	189
Completed	42	9
Not completed	142	182
Death	11	7
Withdrawal by Subject	25	26
Protocol Violation	1	-
Progressive Disease	75	103
Randomized but never received study drug	1	2
Lost to Follow-up	-	2
Miscellaneous Reason	29	42

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	OL Phase: Enzalutamide/Enzalutamide

Arm description:

Participants received enzalutamide 160 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.

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

Dosage and administration details:

Participants received enzalutamide 160 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.

Arm title	OL Phase: Bicalutamide/Enzalutamide

Arm description:

Participants received bicalutamide 50 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.

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

Dosage and administration details:

Participants received enzalutamide 160 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.

Number of subjects in period 2	OL Phase: Enzalutamide/Enzalutamide	OL Phase: Bicalutamide/Enzalutamide
Started	42	9
Received Treatment	42	9
Completed	0	0
Not completed	42	9
Death	-	1
Withdrawal by Subject	1	-
Transitioned to 9785-CL-0123 (NCT02960022)	17	5
Progressive Disease	18	3
Miscellaneous Reason	5	-
Lost to Follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Enzalutamide
Reporting group description:	
Participants received enzalutamide 160 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.	
Reporting group title	Bicalutamide
Reporting group description:	
Participants received bicalutamide 50 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.	

Reporting group values	Enzalutamide	Bicalutamide	Total
Number of subjects	184	191	375
Age categorical Units: Subjects			
< 65 years	45	47	92
65-75 years	85	80	165
> 75 years	54	64	118
Age continuous Units: years			
arithmetic mean	70.3	71.1	
standard deviation	± 9.22	± 8.89	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	184	191	375
Race Units: Subjects			
White	172	176	348
Black or African American	8	10	18
Asian	3	2	5
Native Hawaiian or Other Pacific Islander	1	1	2
Other	0	2	2
Ethnicity Units: Subjects			
Not Hispanic or Latino	184	187	371
Hispanic or Latino	0	4	4
LHRH agonist/antagonist initiation or bilateral orchiectomy relative to diagnosis of metastasis Units: Subjects			
Before diagnosis of metastasis	87	76	163
After diagnosis of metastasis	97	115	212

End points

End points reporting groups

Reporting group title	Enzalutamide
Reporting group description:	
Participants received enzalutamide 160 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.	
Reporting group title	Bicalutamide
Reporting group description:	
Participants received bicalutamide 50 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.	
Reporting group title	OL Phase: Enzalutamide/Enzalutamide
Reporting group description:	
Participants received enzalutamide 160 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.	
Reporting group title	OL Phase: Bicalutamide/Enzalutamide
Reporting group description:	
Participants received bicalutamide 50 mg orally once daily until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS consisted of all randomized participants.	
Subject analysis set title	Total Enzalutamide
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received enzalutamide in the double-blind and/or open-label period (including participants who switched from bicalutamide to enzalutamide).	

Primary: Progression Free Survival (PFS) Based on Independent Central Review (ICR) Assessment

End point title	Progression Free Survival (PFS) Based on Independent Central Review (ICR) Assessment
End point description:	
PFS is the time from randomization to the date of the first progression event detected. A progression event was defined as objective evidence of radiographic disease progression based on the assessments by the ICR, skeletal-related event, initiation of new antineoplastic therapy or death by any cause, whichever occurred first. Radiographic disease progression was defined as either a progression in soft tissue on computed tomography (CT)/magnetic resonance imaging (MRI) scan according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and/or a progression in bone lesions on bone scan (≥ 2 new bone lesions) confirmed by the next bone scan. A skeletal-related event was any radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression or change in antineoplastic therapy to treat bone pain. The initiation of new antineoplastic therapy included any new therapy for the treatment of disease progression after the study drug administration started. FAS.	
End point type	Primary
End point timeframe:	
From randomization until the data cut-off date of 19 October 2014, median duration of treatment was 11.6 months in the enzalutamide arm and 5.8 months in the bicalutamide arm.	

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	191		
Units: months				
median (confidence interval 95%)				
months	15.7 (11.5 to 19.4)	5.8 (4.8 to 8.1)		

Statistical analyses

Statistical analysis title	PFS on ICR Enzalutamide Vs. Bicalutamide

Statistical analysis description:

The (unstratified) log-rank test with an overall significance level of 0.05 (two-sided) was used to compare the PFS of enzalutamide to bicalutamide. The (unstratified) Cox proportional hazards model was used to estimate the hazard ratio of enzalutamide to bicalutamide, calculate the corresponding two-sided 95% confidence intervals and test the hypothesis that the hazard ratio is equal to 1.

Comparison groups	Enzalutamide v Bicalutamide
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.57

Secondary: PFS Based on Investigator Assessment

End point title	PFS Based on Investigator Assessment

End point description:

PFS was calculated as the time from randomization to the date of the first progression event detected. A progression event was defined as objective evidence of radiographic disease progression based on the assessments by investigators, skeletal-related event, initiation of new antineoplastic therapy or death by any cause, whichever occurred first. Radiographic disease progression was defined as either a progression in soft tissue on CT/MRI scan according to RECIST 1.1, and/or a progression in bone lesions on bone scan (≥ 2 new bone lesions) confirmed by the next bone scan. A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression or change in antineoplastic therapy to treat bone pain. The initiation of new antineoplastic therapy included any new therapy for the treatment of disease progression after the study drug administration started. The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 19 October 2014, median duration of treatment was 11.6 months in the enzalutamide arm and 5.8 months in the bicalutamide arm.

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	191		
Units: months				
median (confidence interval 95%)				
months	15.3 (11.8 to 19.4)	5.7 (5.4 to 8.1)		

Statistical analyses

Statistical analysis title	PFS on Inv. Assess. Enzalutamide Vs. Bicalutamide
Comparison groups	Bicalutamide v Enzalutamide
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.55

Secondary: Prostate-specific Antigen (PSA) Response by Week 13

End point title	Prostate-specific Antigen (PSA) Response by Week 13

End point description:

The PSA response by Week 13 was defined as the percentage change from Baseline to the smallest PSA value after Baseline (i.e., a decrease of 100% represents the largest possible decrease to a value below the lower limit of quantification) and on or before day 99 (i.e., upper boundary of the Week 13 visit window). For participants with no decrease in PSA post-baseline by Week 13, the PSA response by Week 13 was the smallest increase in PSA up to day 99. For participants with no post-baseline PSA values up to day 99, the PSA response by Week 13 was set to missing. PSA was analyzed at a central laboratory. The analysis population consisted of the FAS with available PSA data.

End point type	Secondary

End point timeframe:

Baseline to Week 13

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	163		
Units: percent change				
median (full range (min-max))				

percent change	-89.03 (-100.0 to 287.7)	0.36 (-98.5 to 25700.0)		

Statistical analyses

Statistical analysis title	PSA Response Enzalutamide Vs. Bicalutamide
Comparison groups	Enzalutamide v Bicalutamide
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon rank sum test

Secondary: Best PSA Response

End point title	Best PSA Response

End point description:

The best PSA response was defined as the percentage change from Baseline to the smallest PSA value after Baseline including PSA results from samples taken after the study drug was stopped. For participants with no decrease in PSA post-baseline, the best PSA response was the smallest increase in PSA. For participants with no post-baseline PSA values, the PSA response was set to missing. PSA was analyzed at a central laboratory. The analysis population consisted of the FAS with available PSA data.

End point type	Secondary

End point timeframe:

Baseline to the data cutoff date of 19 October 2014, median duration of treatment was 11.6 months in the enzalutamide arm and 5.8 months in the bicalutamide arm.

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	168		
Units: percent change				
median (full range (min-max))				
percent change	-92.96 (-100.0 to 287.7)	0.18 (-99.8 to 25700.0)		

Statistical analyses

Statistical analysis title	Best PSA Response Enzalutamide Vs. Bicalutamide
Comparison groups	Bicalutamide v Enzalutamide
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001

Method	Wilcoxon rank sum test

Secondary: Time to PSA Progression

End point title	Time to PSA Progression

End point description:

Time to PSA progression was calculated as the time interval from the date of randomization to the date of first observation of PSA progression. PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir (or above the baseline value for participants who did not have a decline in PSA post-baseline values), and confirmed by a second consecutive PSA assessment at least 3 weeks later. For participants with no documented PSA progression, the time to PSA progression was censored on the date the last PSA sample was taken. Data not reached due to the low number of events is denoted as "99999." The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

From randomization until the data cutoff date of 19 October 2014, median duration of treatment was 11.6 months in the enzalutamide arm and 5.8 months in the bicalutamide arm.

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	191		
Units: months				
median (confidence interval 95%)				
months	19.4 (16.6 to 99999)	5.8 (5.6 to 8.3)		

Statistical analyses

Statistical analysis title	Time to PSA prog. Enzalutamide Vs. Bicalutamide
Comparison groups	Enzalutamide v Bicalutamide
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.39

Secondary: Time to PSA ≤ 4 ng/mL

End point title	Time to PSA ≤ 4 ng/mL

End point description:

Time to PSA ≤ 4 ng/mL was defined as the time interval from the date of randomization to the first date a decline in PSA to a result of 4 ng/mL or below was recorded. In participants without PSA results ≤ 4 ng/mL, the time to PSA ≤ 4 ng/mL was censored on the date of the last PSA sample taken. Participants with a PSA result ≤ 4 ng/mL at Baseline, participants with no Baseline PSA and participants with no post-baseline PSA results were censored on the date of randomization. Data not reached due to the low number of events is denoted as "99999." The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

From randomization until the data cutoff date of 19 October 2014, median duration of treatment was 11.6 months in the enzalutamide arm and 5.8 months in the bicalutamide arm.

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	191		
Units: months				
median (confidence interval 95%)				
months	3.0 (2.9 to 5.6)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Time to PSA Enzalutamide Vs. Bicalutamide
Comparison groups	Bicalutamide v Enzalutamide
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	5.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.18
upper limit	8.09

Secondary: Time to ≥ 30% PSA Decline from Baseline

End point title	Time to ≥ 30% PSA Decline from Baseline

End point description:

The time to ≥ 30% PSA decline from Baseline was defined as the time interval from the date of randomization to the first date a PSA decline from Baseline of at least 30% was recorded. In participants without ≥ 30% PSA decline from Baseline, the time to ≥ 30% PSA decline from Baseline was censored on the date of the last PSA sample taken. Participants who had no Baseline PSA and participants with no post-baseline PSA results were censored on the date of randomization. Data not reached due to the low number of events is denoted as "99999." The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

From randomization until the data cutoff date of 19 October 2014, median duration of treatment was 11.6 months in the enzalutamide arm and 5.8 months in the bicalutamide arm.

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	191		
Units: months				
median (confidence interval 95%)				
months	2.8 (2.8 to 2.8)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Time to ≥ 30% PSA Enzalutamide Vs. Bicalutamide
Comparison groups	Bicalutamide v Enzalutamide
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	5.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.96
upper limit	7.79

Secondary: Time to ≥ 50% PSA Decline from Baseline

End point title	Time to ≥ 50% PSA Decline from Baseline

End point description:

The time to ≥ 50% PSA decline from Baseline was defined as the time interval from the date of randomization to the first date a PSA decline from Baseline of at least 50% was recorded. In participants without ≥ 50% PSA decline from Baseline, the time to ≥ 50% PSA decline from Baseline was censored on the date of the last PSA sample taken. Participants who had no Baseline PSA and participants with no post-baseline PSA results were censored on the date of randomization. Data not reached due to the low number of events is denoted as "99999." The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

From randomization until the data cutoff date of 19 October 2014, median duration of treatment was 11.6 months in the enzalutamide arm and 5.8 months in the bicalutamide arm.

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	191		
Units: months				
median (confidence interval 95%)				
months	2.8 (2.8 to 2.8)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Time to ≥ 50% PSA Enzalutamide Vs. Bicalutamide
Comparison groups	Enzalutamide v Bicalutamide
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	7.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.83
upper limit	10.16

Secondary: Time to ≥ 90% PSA Decline from Baseline

End point title	Time to ≥ 90% PSA Decline from Baseline

End point description:

The time to ≥ 90% PSA decline from Baseline was defined as the time interval from the date of randomization to the first date a PSA decline from Baseline of at least 90% was recorded. In participants without ≥ 90% PSA decline from Baseline, the time to ≥ 90% PSA decline from Baseline was censored on the date of the last PSA sample taken. Participants who had no Baseline PSA and participants with no post-baseline PSA results were censored on the date of randomization. Data not reached due to the low number of events is denoted as "99999." The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

From randomization until the data cutoff date of 19 October 2014, median duration of treatment was 11.6 months in the enzalutamide arm and 5.8 months in the bicalutamide arm.

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	191		
Units: months				
median (confidence interval 95%)				

months	5.4 (3.0 to 5.7)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Time to ≥ 90% PSA Enzalutamide Vs. Bicalutamide
Comparison groups	Enzalutamide v Bicalutamide
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	13.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.23
upper limit	26.79

Secondary: Radiographic PFS Based on ICR Assessment

End point title	Radiographic PFS Based on ICR Assessment

End point description:

Radiographic PFS was calculated as the time interval from the date of randomization to the first date of radiographic disease progression. Radiographic disease progression was defined as either a progression in soft tissue on CT/MRI scan according to RECIST 1.1, and/or a progression in bone lesions (a minimum of 2 new bone lesions as compared to previous scan) on bone scan and confirmed by the next bone scan. Data not reached due to the low number of events is denoted as "99999." The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

From randomization until the data cutoff date of 19 October 2014, median duration of treatment was 11.6 months in the enzalutamide arm and 5.8 months in the bicalutamide arm.

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	191		
Units: months				
median (confidence interval 95%)				
months	99999 (25.6 to 99999)	16.4 (11.1 to 18.1)		

Statistical analyses

Statistical analysis title	Rad. PFS on ICR Enzalutamide Vs. Bicalutamide
Comparison groups	Enzalutamide v Bicalutamide
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.74

Secondary: Percentage of Participants with an Objective Response

End point title	Percentage of Participants with an Objective Response

End point description:

Response assessments were reported by ICR for target lesions in soft tissues and non-target lesions in soft tissues based on CT and/or MRI according to RECIST version 1.1. Objective response was defined as the number of participants achieving either a complete response (CR) or a partial response (PR) based on participant's best overall response assessed at the end of the treatment. The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

From randomization until the data cutoff date of 19 October 2014, median duration of treatment was 11.6 months in the enzalutamide arm and 5.8 months in the bicalutamide arm.

End point values	Enzalutamide	Bicalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	191		
Units: percentage of participants				
number (not applicable)				
percentage of participants	15.8	2.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events

End point title	Percentage of Participants with Adverse Events

End point description:

A serious adverse event was defined as any untoward medical occurrence that at any dose: ● Resulted

in death ● Was life threatening ● Resulted in persistent or significant disability/incapacity ● Resulted in congenital anomaly or birth defect ● Required inpatient hospitalization or led to prolongation of hospitalization ● Other medically important events. Treatment-related indicates adverse events assessed by the Investigator as probably or possibly related to study treatment. The analysis population consisted of the safety analysis set (SAF), which consisted of all participants who had initiated at least 1 dose of study drug. Treatment emergent adverse events (TEAEs) were defined as adverse events (AEs) that started or worsened after starting administration of study drug through end of the study (i.e., the treatment-emergent period).

End point type	Secondary

End point timeframe:

From initiation of study drug up to 30 days after last dose of study drug or the 30-day safety follow-up visit, whichever was last (Median duration of treatment was 11.6 months in enzalutamide arm and 5.8 in bicalutamide arm, 12.6 in the total arm).

End point values	Enzalutamide	Bicalutamide	Total Enzalutamide	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	183	189	192	
Units: percentage of participants				
number (not applicable)				
TEAEs	94.5	94.2	94.8	
Related TEAEs	66.7	49.7	67.2	
Deaths	5.5	1.6	5.7	
Serious TEAEs	33.3	23.8	36.5	
Drug regimen-related serious TEAEs	6.6	3.2	6.8	
TEAEs leading to discontinuation	29.5	23.8	31.3	
Drug regimen-related TEAEs leading to discon.	7.7	5.3	7.8	
TEAEs leading to study drug interruption	10.4	7.9	10.4	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From initiation of study drug start up to 30 days after last dose or 30-day safety follow-up visit, whichever was last. Median duration of treatment (months) DB Phase: Enzalutamide 11.6, Bicalutamide 5.8, OL Phase: Enza./Enza. 21.6, Bica./Enza. 20.9.

Adverse event reporting additional description:

The total number of deaths (all causes) includes deaths reported after the time frame above.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Double-blind Period: Enzalutamide

Reporting group description:

Participants received enzalutamide 160 mg orally once daily in the double-blind period until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.

Reporting group title	Double-blind Period: Bicalutamide

Reporting group description:

Participants received bicalutamide 50 mg orally once daily in the double-blind period until confirmed radiographic disease progression, skeletal-related event or the initiation of a new antineoplastic therapy.

Reporting group title	Open-label Period: Enzalutamide/Enzalutamide

Reporting group description:

Participants received enzalutamide in the double-blind period and received enzalutamide in the open-label period as well.

Reporting group title	Open-label Period: Bicalutamide/Enzalutamide

Reporting group description:

Participants received bicalutamide in the double-blind period and switched over to enzalutamide in the open-label period.

Serious adverse events	Double-blind Period: Enzalutamide	Double-blind Period: Bicalutamide	Open-label Period: Enzalutamide/Enzalutamide
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 141 (34.75%)	43 / 180 (23.89%)	18 / 42 (42.86%)
number of deaths (all causes)	11	7	0
number of deaths resulting from adverse events	10	3	0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	2 / 141 (1.42%)	0 / 180 (0.00%)	0 / 42 (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
Hypotension			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Orthostatic hypotension			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Venous thrombosis limb			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Surgical and medical procedures			
Transurethral prostatectomy			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 141 (0.71%)	1 / 180 (0.56%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basosquamous carcinoma of skin			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Bladder cancer			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences causally related to	0 / 1	0 / 0	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Brain neoplasm malignant			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Cancer pain			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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 lymphocytic leukaemia			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Gastric cancer			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Lung adenocarcinoma			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Malignant neoplasm of conjunctiva			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Malignant neoplasm progression			
subjects affected / exposed	2 / 141 (1.42%)	1 / 180 (0.56%)	3 / 42 (7.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Metastases to lung			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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 spine			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Metastatic pain			
subjects affected / exposed	1 / 141 (0.71%)	1 / 180 (0.56%)	0 / 42 (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
Myelodysplastic syndrome			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Paraneoplastic syndrome			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Penile cancer			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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 cancer			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Ureteric cancer			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Fatigue			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
General physical health deterioration			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Pyrexia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			

Prostatic obstruction			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Craniocerebral injury			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Fall			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Hip fracture			
subjects affected / exposed	1 / 141 (0.71%)	1 / 180 (0.56%)	0 / 42 (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
Rib fracture			
subjects affected / exposed	2 / 141 (1.42%)	0 / 180 (0.00%)	0 / 42 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriogram coronary			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Blood creatinine increased			
subjects affected / exposed	1 / 141 (0.71%)	1 / 180 (0.56%)	0 / 42 (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
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 141 (0.71%)	1 / 180 (0.56%)	0 / 42 (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
Liver function test abnormal			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Angina pectoris			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 141 (1.42%)	1 / 180 (0.56%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	3 / 141 (2.13%)	3 / 180 (1.67%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (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
Coronary artery disease			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Mitral valve incompetence			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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	4 / 141 (2.84%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Sinus tachycardia			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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 extrasystoles			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (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
Ventricular tachyarrhythmia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Congenital, familial and genetic disorders			

Arteriovenous malformation			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Acute respiratory failure			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Dyspnoea			
subjects affected / exposed	2 / 141 (1.42%)	1 / 180 (0.56%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Pleural effusion			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Pneumonia aspiration			
subjects affected / exposed	2 / 141 (1.42%)	1 / 180 (0.56%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Pneumothorax			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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 fibrosis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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	5 / 141 (3.55%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Pancytopenia			
subjects affected / exposed	1 / 141 (0.71%)	1 / 180 (0.56%)	0 / 42 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 141 (1.42%)	0 / 180 (0.00%)	0 / 42 (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
Epiduritis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Hypoglycaemic seizure			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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

Incoherent			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (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
Lacunar infarction			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Paraplegia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Presyncope			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Spinal cord compression			
subjects affected / exposed	1 / 141 (0.71%)	1 / 180 (0.56%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 141 (1.42%)	2 / 180 (1.11%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	1 / 2	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 141 (1.42%)	2 / 180 (1.11%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Diverticulum			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Haematochezia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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 gastrointestinal haemorrhage			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 141 (0.71%)	1 / 180 (0.56%)	0 / 42 (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
Salivary gland calculus			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Bladder obstruction			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Bladder outlet obstruction			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Dysuria			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Haematuria			
subjects affected / exposed	2 / 141 (1.42%)	1 / 180 (0.56%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 141 (0.00%)	2 / 180 (1.11%)	0 / 42 (0.00%)
occurrences causally related to	0 / 0	0 / 2	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive uropathy			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Postrenal failure			
subjects affected / exposed	0 / 141 (0.00%)	2 / 180 (1.11%)	0 / 42 (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
Renal colic			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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 failure			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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 failure acute			
subjects affected / exposed	2 / 141 (1.42%)	0 / 180 (0.00%)	0 / 42 (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
Renal impairment			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress urinary incontinence			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Ureteric dilatation			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Urethral obstruction			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Urinary retention			
subjects affected / exposed	0 / 141 (0.00%)	2 / 180 (1.11%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Back pain			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Bone pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Joint lock			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences causally related to	0 / 1	0 / 0	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Muscular weakness			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Musculoskeletal chest pain			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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 in extremity			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Pathological fracture			
subjects affected / exposed	5 / 141 (3.55%)	2 / 180 (1.11%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 141 (1.42%)	1 / 180 (0.56%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 141 (0.00%)	2 / 180 (1.11%)	0 / 42 (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
Hyponatraemia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Infections and infestations			
Abscess of salivary gland			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Bacteraemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Cellulitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Cystitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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
Diverticulitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (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 viral			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (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
Pneumonia			
subjects affected / exposed	1 / 141 (0.71%)	2 / 180 (1.11%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	2 / 141 (1.42%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-label Period: Bicalutamide/Enzalutamide		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 9 (0.00%)		

occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral artery stenosis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis limb				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Transurethral prostatectomy				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Adenocarcinoma of colon				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Basal cell carcinoma				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Basosquamous carcinoma of skin				

subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bladder cancer				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bowen's disease				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain neoplasm malignant				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cancer pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic lymphocytic leukaemia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colon cancer				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric cancer				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal tract adenoma				
subjects affected / exposed	0 / 9 (0.00%)			

occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm of conjunctiva				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm progression				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to lung				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to spine				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			

deaths causally related to treatment / all	0 / 0			
Myelodysplastic syndrome				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuroendocrine carcinoma				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paraneoplastic syndrome				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Penile cancer				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin cancer				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Superficial spreading melanoma stage unspecified				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Ureteric cancer				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Prostatic obstruction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Craniocerebral injury				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to	0 / 0			

treatment / all				
deaths causally related to treatment / all	0 / 0			
Arteriogram coronary				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eastern Cooperative Oncology Group performance status worsened				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver function test abnormal				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				

subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic valve stenosis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	1 / 9 (11.11%)		

occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Coronary artery disease				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mitral valve incompetence				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sick sinus syndrome				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular extrasystoles				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			

deaths causally related to treatment / all	0 / 1		
Ventricular tachyarrhythmia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	0 / 9 (0.00%)		

occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary fibrosis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile bone marrow aplasia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Convulsion				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epiduritis				
subjects affected / exposed	0 / 9 (0.00%)			

occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemic seizure				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incoherent				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lacunar infarction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paraplegia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			

deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulum				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			

deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Salivary gland calculus				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute prerenal failure				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bladder obstruction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bladder outlet obstruction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysuria				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			

deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstructive uropathy				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postrenal failure				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Renal impairment				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Stress urinary incontinence				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ureteric dilatation				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urethral obstruction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholelithiasis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Bone pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint lock			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal column stenosis			
subjects affected / exposed	0 / 9 (0.00%)		

occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess of salivary gland				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cellulitis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 9 (0.00%)			

occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Double-blind Period: Enzalutamide	Double-blind Period: Bicalutamide	Open-label Period: Enzalutamide/Enzalutamide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 141 (87.23%)	149 / 180 (82.78%)	42 / 42 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	15 / 141 (10.64%)	17 / 180 (9.44%)	12 / 42 (28.57%)
occurrences (all)	16	17	12
Hypotension			
subjects affected / exposed	1 / 141 (0.71%)	2 / 180 (1.11%)	1 / 42 (2.38%)
occurrences (all)	1	2	1
Hypertension			
subjects affected / exposed	18 / 141 (12.77%)	14 / 180 (7.78%)	13 / 42 (30.95%)
occurrences (all)	29	16	16
Surgical and medical procedures			
Jaw operation			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 141 (5.67%)	7 / 180 (3.89%)	2 / 42 (4.76%)
occurrences (all)	10	7	2
Fatigue			
subjects affected / exposed	35 / 141 (24.82%)	38 / 180 (21.11%)	18 / 42 (42.86%)
occurrences (all)	40	45	24
Oedema peripheral			
subjects affected / exposed	10 / 141 (7.09%)	13 / 180 (7.22%)	5 / 42 (11.90%)
occurrences (all)	10	13	5
Pain			
subjects affected / exposed	1 / 141 (0.71%)	8 / 180 (4.44%)	2 / 42 (4.76%)
occurrences (all)	1	8	2
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	9 / 141 (6.38%)	8 / 180 (4.44%)	1 / 42 (2.38%)

occurrences (all)	9	8	1

Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	4 / 141 (2.84%)	2 / 180 (1.11%)	6 / 42 (14.29%)
occurrences (all)	4	2	6
Testicular pain			
subjects affected / exposed	5 / 141 (3.55%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences (all)	5	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Fall			
subjects affected / exposed	9 / 141 (6.38%)	6 / 180 (3.33%)	4 / 42 (9.52%)
occurrences (all)	11	7	6
Rib fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	2 / 42 (4.76%)
occurrences (all)	1	0	2
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 141 (2.13%)	5 / 180 (2.78%)	0 / 42 (0.00%)
occurrences (all)	4	6	0
Blood urea increased			
subjects affected / exposed	0 / 141 (0.00%)	3 / 180 (1.67%)	1 / 42 (2.38%)
occurrences (all)	0	3	1
Haematocrit decreased			
subjects affected / exposed	1 / 141 (0.71%)	2 / 180 (1.11%)	0 / 42 (0.00%)
occurrences (all)	1	2	0
Haemoglobin decreased			
subjects affected / exposed	3 / 141 (2.13%)	5 / 180 (2.78%)	1 / 42 (2.38%)
occurrences (all)	4	5	1
Neutrophil count increased			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Prostatic specific antigen increased			

subjects affected / exposed	4 / 141 (2.84%)	2 / 180 (1.11%)	1 / 42 (2.38%)
occurrences (all)	4	2	1
Red blood cell count increased			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	16 / 141 (11.35%)	15 / 180 (8.33%)	5 / 42 (11.90%)
occurrences (all)	19	15	6
White blood cell count increased			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	2 / 141 (1.42%)	1 / 180 (0.56%)	0 / 42 (0.00%)
occurrences (all)	2	1	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 141 (0.71%)	1 / 180 (0.56%)	1 / 42 (2.38%)
occurrences (all)	1	1	1
Bronchitis chronic			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	5 / 141 (3.55%)	8 / 180 (4.44%)	2 / 42 (4.76%)
occurrences (all)	6	8	2
Dyspnoea			
subjects affected / exposed	7 / 141 (4.96%)	9 / 180 (5.00%)	4 / 42 (9.52%)
occurrences (all)	8	10	8
Nasal congestion			
subjects affected / exposed	2 / 141 (1.42%)	1 / 180 (0.56%)	1 / 42 (2.38%)
occurrences (all)	3	1	1
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	10 / 141 (7.09%)	5 / 180 (2.78%)	4 / 42 (9.52%)
occurrences (all)	10	7	4
Nervous system disorders			
Amnesia			
subjects affected / exposed	4 / 141 (2.84%)	0 / 180 (0.00%)	2 / 42 (4.76%)
occurrences (all)	5	0	2
Dizziness			
subjects affected / exposed	12 / 141 (8.51%)	15 / 180 (8.33%)	6 / 42 (14.29%)
occurrences (all)	15	16	6
Headache			
subjects affected / exposed	11 / 141 (7.80%)	6 / 180 (3.33%)	8 / 42 (19.05%)
occurrences (all)	14	6	10
Lethargy			
subjects affected / exposed	5 / 141 (3.55%)	4 / 180 (2.22%)	3 / 42 (7.14%)
occurrences (all)	6	4	3
Poor quality sleep			
subjects affected / exposed	0 / 141 (0.00%)	2 / 180 (1.11%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Parkinson's disease			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 141 (0.00%)	2 / 180 (1.11%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Glaucoma			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	6 / 141 (4.26%)	7 / 180 (3.89%)	3 / 42 (7.14%)
occurrences (all)	6	7	4
Constipation			
subjects affected / exposed	19 / 141 (13.48%)	24 / 180 (13.33%)	5 / 42 (11.90%)
occurrences (all)	21	25	7
Diarrhoea			
subjects affected / exposed	16 / 141 (11.35%)	15 / 180 (8.33%)	5 / 42 (11.90%)
occurrences (all)	18	18	6
Dyspepsia			
subjects affected / exposed	5 / 141 (3.55%)	4 / 180 (2.22%)	1 / 42 (2.38%)
occurrences (all)	6	4	1
Haemorrhoids			
subjects affected / exposed	1 / 141 (0.71%)	1 / 180 (0.56%)	0 / 42 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	18 / 141 (12.77%)	33 / 180 (18.33%)	10 / 42 (23.81%)
occurrences (all)	22	36	11
Rectal haemorrhage			
subjects affected / exposed	4 / 141 (2.84%)	1 / 180 (0.56%)	1 / 42 (2.38%)
occurrences (all)	4	1	1
Vomiting			
subjects affected / exposed	5 / 141 (3.55%)	9 / 180 (5.00%)	1 / 42 (2.38%)
occurrences (all)	5	10	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	5 / 141 (3.55%)	4 / 180 (2.22%)	1 / 42 (2.38%)
occurrences (all)	5	4	1
Hypertonic bladder			
subjects affected / exposed	2 / 141 (1.42%)	1 / 180 (0.56%)	0 / 42 (0.00%)
occurrences (all)	2	1	0
Haematuria			
subjects affected / exposed	3 / 141 (2.13%)	6 / 180 (3.33%)	5 / 42 (11.90%)
occurrences (all)	5	7	5
Pollakiuria			
subjects affected / exposed	7 / 141 (4.96%)	6 / 180 (3.33%)	1 / 42 (2.38%)

occurrences (all)	7	6	1
Renal failure chronic			
subjects affected / exposed	2 / 141 (1.42%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Urinary retention			
subjects affected / exposed	4 / 141 (2.84%)	5 / 180 (2.78%)	1 / 42 (2.38%)
occurrences (all)	4	7	1
Renal pain			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	1 / 141 (0.71%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 141 (11.35%)	27 / 180 (15.00%)	9 / 42 (21.43%)
occurrences (all)	22	39	11
Bone pain			
subjects affected / exposed	10 / 141 (7.09%)	12 / 180 (6.67%)	1 / 42 (2.38%)
occurrences (all)	13	15	1
Back pain			
subjects affected / exposed	29 / 141 (20.57%)	34 / 180 (18.89%)	11 / 42 (26.19%)
occurrences (all)	39	40	15
Flank pain			
subjects affected / exposed	5 / 141 (3.55%)	2 / 180 (1.11%)	3 / 42 (7.14%)
occurrences (all)	5	2	3
Gouty arthritis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	6 / 141 (4.26%)	4 / 180 (2.22%)	3 / 42 (7.14%)
occurrences (all)	8	4	3
Musculoskeletal pain			
subjects affected / exposed	8 / 141 (5.67%)	17 / 180 (9.44%)	5 / 42 (11.90%)
occurrences (all)	9	23	5

Myalgia			
subjects affected / exposed	9 / 141 (6.38%)	5 / 180 (2.78%)	1 / 42 (2.38%)
occurrences (all)	10	5	2
Neck pain			
subjects affected / exposed	2 / 141 (1.42%)	2 / 180 (1.11%)	4 / 42 (9.52%)
occurrences (all)	3	2	4
Osteoarthritis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	6
Pain in extremity			
subjects affected / exposed	16 / 141 (11.35%)	9 / 180 (5.00%)	5 / 42 (11.90%)
occurrences (all)	22	12	8
Osteonecrosis of jaw			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 141 (0.00%)	1 / 180 (0.56%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	16 / 141 (11.35%)	13 / 180 (7.22%)	2 / 42 (4.76%)
occurrences (all)	19	13	3
Hypercholesterolaemia			
subjects affected / exposed	3 / 141 (2.13%)	1 / 180 (0.56%)	3 / 42 (7.14%)
occurrences (all)	3	1	3
Hyperkalaemia			
subjects affected / exposed	1 / 141 (0.71%)	2 / 180 (1.11%)	2 / 42 (4.76%)
occurrences (all)	1	2	2
Hyperglycaemia			
subjects affected / exposed	2 / 141 (1.42%)	0 / 180 (0.00%)	3 / 42 (7.14%)
occurrences (all)	2	0	4
Hypokalaemia			
subjects affected / exposed	2 / 141 (1.42%)	3 / 180 (1.67%)	1 / 42 (2.38%)
occurrences (all)	2	3	1
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 141 (0.71%)	2 / 180 (1.11%)	3 / 42 (7.14%)
occurrences (all)	1	2	4
Influenza			
subjects affected / exposed	3 / 141 (2.13%)	4 / 180 (2.22%)	1 / 42 (2.38%)
occurrences (all)	4	4	1
Nasopharyngitis			
subjects affected / exposed	11 / 141 (7.80%)	7 / 180 (3.89%)	7 / 42 (16.67%)
occurrences (all)	13	8	9
Osteomyelitis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Scrotal infection			
subjects affected / exposed	0 / 141 (0.00%)	0 / 180 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	7 / 141 (4.96%)	3 / 180 (1.67%)	4 / 42 (9.52%)
occurrences (all)	8	3	4

Non-serious adverse events	Open-label Period: Bicalutamide/Enzalutamide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	5		
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Jaw operation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Testicular pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Rib fracture			
subjects affected / exposed	1 / 9 (11.11%)		

occurrences (all)	1		

Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood urea increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Haematocrit decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Neutrophil count increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Prostatic specific antigen increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Red blood cell count increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 9 (11.11%)		

occurrences (all)	1		

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Bronchitis chronic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
Lethargy			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Poor quality sleep			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Parkinson's disease			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Glaucoma			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Haemorrhoids			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	0 / 9 (0.00%)		

occurrences (all)	0		
Rectal haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypertonic bladder			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Haematuria			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Renal failure chronic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Renal pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Arthralgia				
subjects affected / exposed	5 / 9 (55.56%)			
occurrences (all)	6			
Bone pain				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Back pain				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Flank pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Gouty arthritis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Musculoskeletal chest pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Musculoskeletal pain				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Myalgia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Neck pain				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Osteoarthritis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Pain in extremity				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Osteonecrosis of jaw				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			

Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Osteomyelitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Scrotal infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)		

occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 December 2010	The changes include: • Increased the number of eligible patients enrolled to 370 to ensure the target number of events was achieved • Removed planned interim analysis because it was not required • Clarified definition of mg abbreviation • Corrected time points for administering the BPI-SF • Updated sample size calculation considerations to ensure that the target number of progression events was achieved • Expanded the definition of metastatic disease in inclusion criterion 5 to include patients with significant nodal metastases • Amended exclusion criterion 12 to liberalize prior use of antiandrogens based on clinical practice/treatment paradigm for this patient population • Lengthened visit window at weeks 13 and 25 to allow for CT/MRI and bone scan imaging to be scheduled and performed in association with the study visit • Added instruction for Patient Dosing Diary to collect information on medication dosing and food intake prior to pharmacokinetic sampling • Updated contact details of key sponsor personnel for safety information • Separated out radiographic disease progression and a skeletal-related event as reasons for discontinuation of study drug to ensure consistency throughout protocol • Updated name of software package used to perform sample size calculations • Updated text regarding analysis of pharmacokinetics • Updated text regarding imputation of missing data • Added option to allow patients to resume study medication at a lower dose in order to reduce the likelihood the patient experienced a similar AE of grade 3 or greater toxicity • Removed reference that blood sample for CTC enumeration was to be collected at screening • Added testosterone laboratory test to be performed at screening for assessment of inclusion criterion 4 • Updated Section header 2.3.4 T2:ERG, and subsequent section header, to accurately reflect secondary heading of 'Exploratory Variables'
07 December 2010	Continued: • Removed reference that laboratory tests were to be performed at a local laboratory because they were to be performed at a central laboratory instead • Clarified that Data Monitoring Committee (i.e., DSMB) was to monitor only safety data on an ongoing basis • Defined the QRS abbreviation as QRS interval • Made administrative changes and typographical corrections.
16 January 2012	The changes include: • Revised exclusion criteria to reflect the current medical practices and use of antiandrogens in the study patient population • Included information on the assessment of potential drug induced liver injury to ensure complete review of all relevant discontinuation criteria by the investigator • Updated the number of investigational sites • Included updated safety reporting information to accurately reflect the serious adverse event (SAE) reporting process • Revised process for ECG collection to remove sponsor collection of copies of the ECGs • Clarified under what circumstances the sponsor could break the treatment code • Updated the appendix for elements of Informed Consent to comply with 42 U.S.C 282(j)(1)(A) • Updated the section on publication of the study to reflect the current Astellas publication policy • Updated the safety language in Appendices 2 and 10 for consistency with FDA Guidance for Industry and Investigators Drug Induced Liver Injury, FDA Jul 2009 • Made typographical corrections.

19 August 2013	The changes include: ● Revised confirmatory scan requirements to clarify timing, qualifications and baseline time point ● Clarified inclusion criterion 5 to distinguish requirement of metastatic disease at the time of the screening visit ● Added inclusion criterion 11 detailing the appropriate contraception methods available for participants of the clinical trial ● Revised exclusion criterion 10, correcting the dosage unit for spironolactone from 50 mg/kg to 50 mg/day ● Added statement indicating that waivers to the selection criteria will not be allowed ● Added denosumab to list of allowed medications and radiopharmaceuticals to the list of prohibited medications ● Revised information regarding cytochrome P450 (CYP) pathways used in the metabolism of enzalutamide and bicalutamide to state caution should be exercised when bicalutamide is co-administered with CYP3A4 substrates ● Provided clarity regarding the requirements for chest imaging and dictated the possibility for continued imaging for ongoing patients ● Added dosing diary dispensing and collection to the Schedule of Assessments ● Updated nonclinical and clinical data and safety information in the introduction sections to reflect the most current data available for enzalutamide ● Updated the risk benefit statement to reflect the most current safety data available for enzalutamide ● Updated the test drug section to reflect the most current clinical data available for enzalutamide ● Included instructions for restarting study drug in event of dose interruption due to a specified toxicity ● Updated drug-drug interaction information to reflect the most current safety data available for enzalutamide ● Added histological and clinical to diagnosis types documented at screening. ● Revised text describing body systems (without adding new body systems). Clarified the requirements for performing digital rectal examination (DRE)
19 August 2013	Continued: ● Updated definition of AEs to include undergoing study procedures. ● Included additional information regarding safety events of interest that could require expedited reporting and/or safety evaluation and their reporting requirements ● To provide clarity, rewrote section on Supply of New Information Affecting Conduct of the Study ● Added a new section and related appendix for common SAEs ● Defined protocol deviations and clarified the process of identifying the deviations by category/type in the summary tables ● Added a new section clarifying what was considered a deviation and explaining responsibilities of investigators ● Added a new section to define the end of trial in all participating countries as the 'last patient's last visit' ● Specified signatories permitted to sign the CSR ● Deleted appendices that are not mandated by regulations (Appendix 12.2 Events Always Considered to be Serious) or are covered in ICH GCP and master informed consent form (ICF) (Appendix 12.3 Elements of Informed Consent; Appendix 12.4 Elements of HIPAA Authorization [US Site Only]) ● Made administrative changes and typographical corrections.

19 July 2014	The changes include: • Added an open-label extension period to ensure continuing treatment of patients receiving clinical benefit from study participation after unblinding. Descriptions of double-blind and open-label period were added to the synopsis to clearly identify and delineate the study periods. Appendix 9 Open-Label Period was added to the protocol to describe the procedures associated with the open-label period in detail • Added seizure as a possible reason for discontinuation in the eligibility criteria • Added a statement to allow the final efficacy analysis to be performed when 85% power is reached and added the corresponding minimum number of progression events • Added text regarding collection of T2:ERG tissue sample • Revised the groupings of Gleason score and added the previous use of antiandrogen therapy as variables in the subgroup analyses • Revised CTC conversion text • For consistency with the revised SAP, added protocol deviation category PD5 Other to capture protocol deviations that fall outside the standard categories • Corrected list of common SAEs with the appropriate list of common AEs specific to enzalutamide • Made administrative changes and typographical corrections.
24 June 2016	The changes include: • Revised the study design; patients who were continuing to derive clinical benefit from treatment with enzalutamide based on the investigator's medical opinion and had not met any of the treatment discontinuation criteria, as outlined in Section 12.9 of the protocol, may have been eligible to continue receiving treatment with enzalutamide in the open-label extension study 9785-CL-0123 upon activation of this study at the participating institution. Patients who chose not to participate or were not eligible for study 9785-CL-0123 completed their participation in study 9785-CL-0222 by completing the 30 day safety follow up visit • Updated sponsor contact information; details for 24 hour-Contact for SAEs, Clinical Research Contacts and Medical Monitors were updated • Made administrative changes and typographical corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported