



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Phase IIIb Study of the Efficacy and Safety of Continuing Enzalutamide in Chemotherapy Naïve Metastatic Castration Resistant Prostate Cancer Patients Treated with Docetaxel plus Prednisolone Who Have Progressed on Enzalutamide Alone

Summary

EudraCT number	2013-004711-50
Trial protocol	CZ IT GB DE SE ES GR BE FR AT PL NL
Global end of trial date	

Results information

Result version number	v1
This version publication date	15 October 2021
First version publication date	15 October 2021

Trial information

Trial identification

Sponsor protocol code	9785-MA-1001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02288247
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe Ltd. (APEL)
Sponsor organisation address	300 Dashwood Lang Road, Bourne Business Park, Addlestone, United Kingdom, KT15 2NX
Public contact	Clinical Trial Disclosure, Astellas Pharma Europe Ltd. (APEL), +31 0 71 5455 050, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe Ltd. (APEL), +31 0 71 5455 050, 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	Interim
Date of interim/final analysis	30 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of continuing treatment with enzalutamide after adding docetaxel and prednisolone versus placebo plus docetaxel and prednisolone, as measured by Progression Free Survival (PFS) in participants with chemotherapy-naïve metastatic Castration-Resistant Prostate Cancer (mCRPC) with progression during treatment with enzalutamide alone.

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	01 December 2014
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	Austria: 9
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Czechia: 30
Country: Number of subjects enrolled	France: 69
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Greece: 18
Country: Number of subjects enrolled	Italy: 60
Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Poland: 70
Country: Number of subjects enrolled	Russian Federation: 54
Country: Number of subjects enrolled	Spain: 81
Country: Number of subjects enrolled	Sweden: 60
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Turkey: 55
Country: Number of subjects enrolled	United Kingdom: 89

Worldwide total number of subjects	688
EEA total number of subjects	487

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	128
From 65 to 84 years	541
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

Male participants with metastatic Castration-Resistant Prostate Cancer (mCRPC) who had progressed while on luteinizing hormone-releasing hormone (LHRH) agonist/antagonist or after receiving a bilateral orchiectomy and had not yet received chemotherapy were enrolled in the study.

Pre-assignment

Screening details:

Following Screening, participants received open-label (OL) treatment with enzalutamide in period 1 followed by period 2 randomized double-blind (DB) treatment with continued enzalutamide or placebo, adding with docetaxel and prednisolone. Participants were stratified by disease progression in Period 1 (evidence of radiographic progression or not).

Period 1

Period 1 title	Period 1: OL Treatment (Max: 315 weeks)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Period 1: Enzalutamide
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Arm description:

Participants received an OL treatment with enzalutamide 160 milligrams (mg) capsules, orally once daily from day 1 in period 1 until randomization to period 2 treatment, confirmation of ineligibility for period 2 treatment, intolerable toxicity, withdrawal, or death, whichever occurred first.

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.

Number of subjects in period 1	Period 1: Enzalutamide
Started	688
Treated	687
Completed	41
Not completed	647
Death	35
Progressive Disease	392
Not specified	106
Adverse event	52
Withdrawal by Subject	52
Lost to follow-up	1

Protocol deviation	9
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Period 2

Period 2 title	Period 2: DB Treatment (Max: 180 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Period 2: Enzalutamide

Arm description:

Participants with confirmed disease progression on enzalutamide in period 1 and who continued to meet all eligibility criteria received enzalutamide 160 mg capsules, orally once daily in combination with docetaxel 75 mg/m² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, DB treatment in period 2. Docetaxel and prednisolone were administered up to 10 cycles (1 cycle= 3 weeks) or additional cycles as assessed by the investigator and enzalutamide was administered until disease progression, intolerable toxicity, withdrawal or death, whichever occurred first. Participants could continue the extension period if they were still receiving study drug in Period 1 when enrollment to Period 2 closed or when the data cut-off for analysis was reached in Period 2, until the investigator or participant decided to stop or disease progression, intolerable toxicity, withdrawal or death, whichever occurred first.

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.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received prednisolone 5 mg orally twice daily.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received docetaxel 75 mg/m² in a one-hour infusion every 3 weeks

Arm title	Period 2: Placebo
Arm description:	
Participants with confirmed disease progression on enzalutamide in period 1 and who continued to meet all eligibility criteria received placebo matched to enzalutamide, orally once daily in combination with docetaxel 75 mg/m ² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, in DB treatment period 2. Docetaxel and prednisolone were administered up to 10 cycles (1 cycle= 3 weeks) or additional cycles as assessed by the investigator and enzalutamide was administered until disease progression, intolerable toxicity, withdrawal or death, whichever occurred first. Participants could continue the extension period if they were still receiving study drug in Period 1 when enrollment to Period 2 closed or when the data cut-off for analysis was reached in Period 2, until the investigator or participant decided to stop or disease progression, intolerable toxicity, withdrawal or death, whichever occurred first.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Participants received placebo matched to enzalutamide orally once daily	

Number of subjects in period 2^[1]	Period 2: Enzalutamide	Period 2: Placebo
Started	1	1
Completed	1	1
Not completed	136	135
Randomized but not treated	1	-
Death	8	4
Progressive Disease	87	94
Not specified	20	21
Adverse event	10	8
Withdrawal by Subject	7	7
Lost to follow-up	1	-
Protocol deviation	2	1
Joined	136	135
Joined period 2 from period 1	136	135

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants who did not complete Period 1 could also join Period 2.

Baseline characteristics

Reporting groups

Reporting group title	Period 1: OL Treatment (Max: 315 weeks)
Reporting group description:	
Participants received an OL treatment with enzalutamide 160 mg capsules, orally once daily from day 1 in period 1 until randomization to period 2 treatment, confirmation of ineligibility for period 2 treatment, intolerable toxicity, withdrawal, or death, whichever occurred first. Participants with confirmed disease progression on enzalutamide in period 1 and who continued to meet all eligibility criteria received enzalutamide 160 mg capsules/placebo matched to enzalutamide, orally once daily in combination with docetaxel 75 mg/m ² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, DB treatment in period 2. Docetaxel and prednisolone were administered up to 10 cycles (1 cycle= 3 weeks) or additional cycles as assessed by the investigator and enzalutamide was administered until disease progression, intolerable toxicity, withdrawal or death, whichever occurred first.	

Reporting group values	Period 1: OL Treatment (Max: 315 weeks)	Total	
Number of subjects	688	688	
Age categorical Units: Subjects			

Age			
Number of participants analyzed for age (continuous) data is 687.			
Units: years			
arithmetic mean	71.0		
standard deviation	± 7.8	-	
Sex			
Units: Subjects			
Male	687	687	
Unknown	1	1	
Analysis Race			
Units: Subjects			
Black	5	5	
Other	1	1	
White	681	681	
Unknown	1	1	

End points

End points reporting groups

Reporting group title	Period 1: Enzalutamide
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Reporting group description:

Participants received an OL treatment with enzalutamide 160 milligrams (mg) capsules, orally once daily from day 1 in period 1 until randomization to period 2 treatment, confirmation of ineligibility for period 2 treatment, intolerable toxicity, withdrawal, or death, whichever occurred first.

Reporting group title	Period 2: Enzalutamide
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Reporting group description:

Participants with confirmed disease progression on enzalutamide in period 1 and who continued to meet all eligibility criteria received enzalutamide 160 mg capsules, orally once daily in combination with docetaxel 75 mg/m² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, DB treatment in period 2. Docetaxel and prednisolone were administered up to 10 cycles (1 cycle= 3 weeks) or additional cycles as assessed by the investigator and enzalutamide was administered until disease progression, intolerable toxicity, withdrawal or death, whichever occurred first. Participants could continue the extension period if they were still receiving study drug in Period 1 when enrollment to Period 2 closed or when the data cut-off for analysis was reached in Period 2, until the investigator or participant decided to stop or disease progression, intolerable toxicity, withdrawal or death, whichever occurred first.

Reporting group title	Period 2: Placebo
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Reporting group description:

Participants with confirmed disease progression on enzalutamide in period 1 and who continued to meet all eligibility criteria received placebo matched to enzalutamide, orally once daily in combination with docetaxel 75 mg/m² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, in DB treatment period 2. Docetaxel and prednisolone were administered up to 10 cycles (1 cycle= 3 weeks) or additional cycles as assessed by the investigator and enzalutamide was administered until disease progression, intolerable toxicity, withdrawal or death, whichever occurred first. Participants could continue the extension period if they were still receiving study drug in Period 1 when enrollment to Period 2 closed or when the data cut-off for analysis was reached in Period 2, until the investigator or participant decided to stop or disease progression, intolerable toxicity, withdrawal or death, whichever occurred first.

Subject analysis set title	Enzalutamide
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants with confirmed disease progression on enzalutamide in period 1 and who continued to meet all eligibility criteria received enzalutamide 160 mg capsules, orally once daily in combination with docetaxel 75 mg/m² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, in DB treatment period 2. Docetaxel and prednisolone were administered up to 10 cycles (1 cycle= 3 weeks) or additional cycles as assessed by the investigator and enzalutamide was administered until disease progression, intolerable toxicity, withdrawal or death, whichever occurred first. Participants could continue the extension period if they were still receiving study drug in Period 1 when enrollment to Period 2 closed or when the data cut-off for analysis was reached in Period 2, until the investigator or participant decided to stop or disease progression, intolerable toxicity, withdrawal or death, whichever occurred first.

Subject analysis set title	Placebo
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants with confirmed disease progression on enzalutamide in period 1 and who continued to meet all eligibility criteria received placebo matched to enzalutamide, orally once daily in combination with docetaxel 75 mg/m² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, in DB treatment period 2. Docetaxel and prednisolone were administered up to 10 cycles (1 cycle= 3 weeks) or additional cycles as assessed by the investigator and enzalutamide was administered until disease progression, intolerable toxicity, withdrawal or death, whichever occurred first. Participants could continue the extension period if they were still receiving study drug in Period 1 when enrollment to Period 2 closed or when the data cut-off for analysis was reached in Period 2, until the investigator or participant decided to stop or disease progression, intolerable toxicity, withdrawal or death, whichever occurred first.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
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End point description:

PFS: time from randomization (Period 2 Week 1) to earliest progression event. Progression is defined as radiographic progression, unequivocal clinical progression, or death on study. Radiographic progression is defined for bone disease by appearance of ≥ 2 new lesions on whole-body radionuclide bone scan per Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria (i.e., unconfirmed progressive disease) that needs to be confirmed in the next assessment (i.e., progressive disease in the next assessment) or for soft tissue disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Unequivocal clinical progression is defined as new onset cancer pain requiring chronic administration of opiate analgesia or deterioration from prostate cancer of Eastern Cooperative Oncology Group (ECOG) performance status score to ≥ 3 , or initiation of subsequent lines of cytotoxic chemotherapy or radiation therapy or surgical intervention due to complications of tumor progression.

End point type	Primary
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End point timeframe:

From date of randomization to the earliest of either documented disease progression (median duration: 35 weeks)

End point values	Enzalutamide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136 ^[1]	135 ^[2]		
Units: months				
median (confidence interval 95%)	9.53 (8.25 to 10.87)	8.28 (6.28 to 8.71)		

Notes:

[1] - Full Analysis Set (FAS) included all randomized participants who received at least one dose of IMP.

[2] - Full Analysis Set (FAS) included all randomized participants who received at least one dose of IMP.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 ^[3]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.96

Notes:

[3] - From the Cox proportional hazards model with covariates for treatment and disease progression in Period 1 (radiographic, nonradiographic).

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

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

Time to PSA progression, defined as the time from randomization (Period 2 Week 1) to the date of the

first PSA value in Period 2 demonstrating progression (Period 2). The PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir recorded in Period 2 is documented, which must be confirmed by a second consecutive value obtained at least 3 weeks later. FAS.

End point type	Secondary
End point timeframe:	
From date of randomization to the first PSA value (median duration: 35 weeks)	

End point values	Enzalutamide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136	135		
Units: months				
median (confidence interval 95%)	8.44 (8.18 to 9.00)	6.24 (5.42 to 8.31)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[4]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.82

Notes:

[4] - From the Cox proportional hazards model with covariates for treatment and disease progression in Period 1 (radiographic, nonradiographic).

Secondary: Prostate-specific Antigen (PSA) Response

End point title	Prostate-specific Antigen (PSA) Response
End point description:	
PSA response, defined as a decrease in percentage change from randomization (Period 2 Week 1) of 50% or more. PSA response was derived at Week 13 and at any time after randomization in Period 2. PSA response at any time is defined as a decrease in percentage change from randomization (Period 2 Week 1) at any time after randomization of 50% or more. Percentage of participants with PSA response was reported. FAS.	
End point type	Secondary
End point timeframe:	
Randomization, Week 13, any time after randomization in Period 2 (median of 35 weeks)	

End point values	Enzalutamide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136	135		
Units: percentage of participants				
number (not applicable)				
Week 13	44.9	25.2		
Any time after randomization (median of 35 weeks)	55.9	37.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
End point description: ORR, defined as the best overall radiographic response after randomization (Period 2 Week 1) as per Investigator assessments of response for soft tissue disease per RECIST 1.1, in participants who had a measurable tumor. Percentage of participants with ORR were reported. FAS.	
End point type	Secondary
End point timeframe: From date of randomization up to median duration of 35 weeks	

End point values	Enzalutamide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136	135		
Units: percentage of participants				
number (not applicable)	31.6	25.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.142 ^[5]
Method	Cochran-Mantel-Haenszel

Notes:

[5] - From the Cochran-Mantel-Haenszel test stratified by disease progression (radiographic, non-radiographic) in Period 1.

Secondary: Time to pain progression

End point title	Time to pain progression
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End point description:

Time to an increase of $\geq 30\%$ from randomization (Period 2 Week 1) in average BPI-SF item scores (items 3,4,5,6) at two consecutive evaluations ≥ 3 weeks apart without decrease in analgesic score according to World Health Organization (WHO). Only participants with average pain intensity item score ≥ 4 were considered. BPI-SF: an instrument to document pain-related functional impairment, contains 7 questions which included pain intensity [(items 3, 4, 5 and 6): worst pain, least pain, average pain and current pain, with scales from 0 (no pain) to 10 (pain as bad as you can imagine)] and pain interference [(items 9A to 9G): general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life, with scales from 0 (does not interfere) to 10 (completely interferes)]. BPI-SF total score for pain intensity was calculated as the mean of the 4 scores for the 4 items. FAS. "99999" = none of the participants met the criteria for pain progression.

End point type	Secondary
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End point timeframe:

From date of randomization up to median duration of 35 weeks

End point values	Enzalutamide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139	135		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to opiate use for cancer-related pain

End point title	Time to opiate use for cancer-related pain
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End point description:

Time to opiate use for cancer-related pain, defined as the time from randomization (Period 2 Week 1) to initiation of chronic administration of opiate analgesia [parenteral opiate use for ≥ 7 days or use of WHO Analgesic Ladder Level 3 oral opiates for ≥ 3 weeks]. FAS. "99999" = none of the participants had cancer-related pain.

End point type	Secondary
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End point timeframe:

From date of randomization up to median duration of 35 weeks

End point values	Enzalutamide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136	135		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first Skeletal-related Event (SRE)

End point title	Time to first Skeletal-related Event (SRE)
End point description:	
Time to first SRE, defined as the time from randomization (Period 2 Week 1) to radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. FAS. "99999"= upper limit of 95% confidence interval was not estimable due to insufficient number of events.	
End point type	Secondary
End point timeframe:	
From date of randomization up to median duration of 35 weeks	

End point values	Enzalutamide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136	135		
Units: months				
median (confidence interval 95%)	21.98 (15.18 to 99999)	17.35 (17.35 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Enzalutamide v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.994 ^[6]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	2.13

Notes:

[6] - From the Cox proportional hazards model with covariates for treatment and disease progression in Period 1 (radiographic, nonradiographic).

Secondary: Change from Baseline in Functional Assessment of Cancer Therapy - Prostate (FACT-P)

End point title	Change from Baseline in Functional Assessment of Cancer Therapy - Prostate (FACT-P)
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End point description:

The FACT-P quality of life questionnaire is a multi-dimensional, self-reported quality of life instrument specifically designed for use with prostate cancer participants. It consists of 27 core items which assess participant function in four domains: physical well-being (PWB) (7 items), social/family well-being (SWB) (7 items), emotional well-being (EWB) (6 items), and functional well-being (FWB) (7 items), which is further supplemented by 12 site-specific items to assess for prostate-related symptoms (Prostate Cancer Subscale [PCS]). Each item is rated on a 0 to 4 Likert-type scale (0=Not at all, 1=A little bit, 2=Some-what, 3=Quite a bit, 4=Very much), and then combined to a global quality of life score ranging between 0 to 156, with higher scores representing better quality of life. Participants in the FAS population with available data were analyzed. "99999"= No participants/only 1 participant was analyzed for the specified timepoint.

End point type	Secondary
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End point timeframe:

Period 2: Baseline, weeks 1, 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157, 169, 181

End point values	Enzalutamide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	133		
Units: score on a scale				
arithmetic mean (standard deviation)				
EWB: Baseline (n= 122, 132)	0.00 (± 0.00)	0.00 (± 0.00)		
EWB: Change at Week 1 (n= 104, 115)	0.00 (± 0.00)	0.00 (± 0.00)		
EWB: Change at Week 13 (n= 88, 99)	1.15 (± 4.15)	1.36 (± 3.63)		
EWB: Change at Week 25 (n= 60, 64)	0.69 (± 3.85)	1.03 (± 3.58)		
EWB: Change at Week 37 (n= 55, 45)	1.91 (± 3.85)	1.43 (± 3.73)		
EWB: Change at Week 49 (n= 38, 22)	1.22 (± 3.62)	0.73 (± 4.24)		
EWB: Change at Week 61 (n= 18, 6)	0.59 (± 4.52)	2.00 (± 3.58)		
EWB: Change at Week 73 (n= 11, 1)	1.69 (± 3.13)	-1.00 (± 99999)		
EWB: Change at Week 85 (n= 5, 1)	1.00 (± 4.06)	-5.00 (± 99999)		
EWB: Change at Week 97 (n= 4, 0)	3.90 (± 4.75)	99999 (± 99999)		
EWB: Change at Week 109 (n= 3, 0)	2.93 (± 3.49)	99999 (± 99999)		
EWB: Change at Week 121 (n= 2, 0)	4.00 (± 2.83)	99999 (± 99999)		
EWB: Change at Week 133 (n= 2, 0)	2.00 (± 0.00)	99999 (± 99999)		
EWB: Change at Week 145 (n= 1, 0)	2.00 (± 99999)	99999 (± 99999)		
EWB: Change at Week 157 (n= 1, 0)	2.00 (± 99999)	99999 (± 99999)		
EWB: Change at Week 169 (n= 1, 0)	1.00 (± 99999)	99999 (± 99999)		
EWB: Change at Week 181 (n= 1, 0)	2.00 (± 99999)	99999 (± 99999)		

FWB: Baseline (n= 122, 132)	0.0000 (± 0.0000)	0.0000 (± 0.0000)		
FWB: Change at Week 1 (n= 104, 115)	0.0000 (± 0.0000)	0.0000 (± 0.0000)		
FWB: Change at Week 13 (n= 88, 99)	-1.8144 (± 5.0586)	-0.3121 (± 4.7437)		
FWB: Change at Week 25 (n= 60, 64)	-2.4472 (± 5.2508)	-0.8229 (± 5.2563)		
FWB: Change at Week 37 (n= 55, 45)	-1.5697 (± 6.3251)	-0.1459 (± 3.2857)		
FWB: Change at Week 49 (n= 38, 22)	-1.1579 (± 6.7284)	-1.3818 (± 4.5238)		
FWB: Change at Week 61 (n= 18, 6)	0.0000 (± 4.7651)	-2.3333 (± 2.8048)		
FWB: Change at Week 73 (n= 11, 1)	-1.8182 (± 3.5726)	-2.0000 (± 99999)		
FWB: Change at Week 85 (n= 5, 1)	1.2000 (± 4.8166)	0.0000 (± 99999)		
FWB: Change at Week 97 (n= 4, 0)	-0.5000 (± 1.7321)	99999 (± 99999)		
FWB: Change at Week 109 (n= 3, 0)	-1.3333 (± 3.2146)	99999 (± 99999)		
FWB: Change at Week 121 (n= 2, 0)	-1.5000 (± 0.7071)	99999 (± 99999)		
FWB: Change at Week 133 (n= 2, 0)	-0.5000 (± 2.1213)	99999 (± 99999)		
FWB: Change at Week 145 (n= 1, 0)	-2.0000 (± 99999)	99999 (± 99999)		
FWB: Change at Week 157 (n= 1, 0)	0.0000 (± 99999)	99999 (± 99999)		
FWB: Change at Week 169 (n= 1, 0)	-1.0000 (± 99999)	99999 (± 99999)		
FWB: Change at Week 181 (n= 1, 0)	0.0000 (± 99999)	99999 (± 99999)		
Global Score: Baseline (n= 121, 129)	0.0000 (± 0.0000)	0.0000 (± 0.0000)		
Global Score: Change at Week 1 (n= 104, 113)	0.0000 (± 0.0000)	0.0000 (± 0.0000)		
Global Score: Change at Week 13 (n= 84, 95)	-0.7836 (± 17.7356)	1.7986 (± 16.3294)		
Global Score: Change at Week 25 (n= 58, 61)	-5.9204 (± 18.2107)	1.0762 (± 17.0168)		
Global Score: Change at Week 37 (n= 52, 43)	-1.5351 (± 20.3721)	0.1649 (± 15.8335)		
Global Score: Change at Week 49 (n= 37, 21)	-4.4880 (± 24.6865)	-4.6202 (± 17.9530)		
Global Score: Change at Week 61 (n= 17, 6)	-0.2957 (± 17.6915)	6.0939 (± 8.8208)		
Global Score: Change at Week 73 (n= 11, 0)	-0.3917 (± 18.3346)	99999 (± 99999)		
Global Score: Change at Week 85 (n= 5, 0)	1.7636 (± 11.7476)	99999 (± 99999)		
Global Score: Change at Week 97 (n= 4, 0)	6.2864 (± 9.8128)	99999 (± 99999)		
Global Score: Change at Week 109 (n= 3, 0)	-2.7333 (± 17.6299)	99999 (± 99999)		
Global Score: Change at Week 121 (n= 1, 0)	4.0000 (± 99999)	99999 (± 99999)		
Global Score: Change at Week 133 (n= 2, 0)	-7.0000 (± 4.2426)	99999 (± 99999)		
Global Score: Change at Week 145 (n= 1, 0)	-11.0000 (± 99999)	99999 (± 99999)		

Global Score: Change at Week 157 (n= 1, 0)	-1.0000 (± 99999)	99999 (± 99999)		
Global Score: Change at Week 169 (n= 1, 0)	-10.0000 (± 99999)	99999 (± 99999)		
Global Score: Change at Week 181 (n= 1, 0)	-4.0000 (± 99999)	99999 (± 99999)		
PWB: Baseline (n= 124, 133)	0.0000 (± 0.0000)	0.0000 (± 0.0000)		
PWB: Change at Week 1 (n= 106, 115)	0.0000 (± 0.0000)	0.0000 (± 0.0000)		
PWB: Change at Week 13 (n= 90, 100)	-1.3322 (± 6.0823)	-0.6347 (± 4.4643)		
PWB: Change at Week 25 (n= 62, 65)	-3.1317 (± 6.5208)	-0.4590 (± 4.2887)		
PWB: Change at Week 37 (n= 56, 45)	-2.1786 (± 5.5611)	-0.9556 (± 4.3691)		
PWB: Change at Week 49 (n= 38, 23)	-2.5316 (± 8.0882)	-1.3913 (± 6.1625)		
PWB: Change at Week 61 (n= 18, 6)	-1.3889 (± 6.9886)	1.3333 (± 3.8297)		
PWB: Change at Week 73 (n= 11, 1)	-0.3636 (± 8.0408)	3.0000 (± 99999)		
PWB: Change at Week 85 (n= 5, 1)	1.0000 (± 10.3682)	3.0000 (± 99999)		
PWB: Change at Week 97 (n= 4, 0)	1.7500 (± 10.4363)	99999 (± 99999)		
PWB: Change at Week 109 (n= 3, 0)	-0.6667 (± 13.6504)	99999 (± 99999)		
PWB: Change at Week 121 (n= 2, 0)	-4.0000 (± 1.4142)	99999 (± 99999)		
PWB: Change at Week 133 (n= 2, 0)	-4.5000 (± 0.7071)	99999 (± 99999)		
PWB: Change at Week 145 (n= 1, 0)	-4.0000 (± 99999)	99999 (± 99999)		
PWB: Change at Week 157 (n= 1, 0)	0.0000 (± 99999)	99999 (± 99999)		
PWB: Change at Week 169 (n= 1, 0)	-4.0000 (± 99999)	99999 (± 99999)		
PWB: Change at Week 181 (n= 1, 0)	-2.0000 (± 99999)	99999 (± 99999)		
PCS: Baseline (n= 123, 130)	0.0000 (± 0.0000)	0.0000 (± 0.0000)		
PCS: Change at Week 1 (n= 106, 113)	0.0000 (± 0.0000)	0.0000 (± 0.0000)		
PCS: Change at Week 13 (n= 86, 95)	1.1842 (± 6.1843)	1.6011 (± 6.0731)		
PCS: Change at Week 25 (n= 60, 63)	-0.4775 (± 6.2665)	1.8632 (± 6.3433)		
PCS: Change at Week 37 (n= 53, 44)	-1.1433 (± 7.3006)	0.6988 (± 7.1353)		
PCS: Change at Week 49 (n= 37, 22)	-1.8465 (± 8.6083)	-0.7223 (± 7.8442)		
PCS: Change at Week 61 (n= 17, 6)	0.3690 (± 6.0031)	4.2606 (± 3.1148)		
PCS: Change at Week 73 (n= 11, 0)	0.9174 (± 7.8001)	99999 (± 99999)		
PCS: Change at Week 85 (n= 5, 0)	2.1636 (± 5.6123)	99999 (± 99999)		
PCS: Change at Week 97 (n= 4, 0)	3.8864 (± 3.3380)	99999 (± 99999)		
PCS: Change at Week 109 (n= 3, 0)	-1.6667 (± 5.8595)	99999 (± 99999)		

PCS: Change at Week 121 (n= 1, 0)	2.0000 (± 99999)	99999 (± 99999)		
PCS: Change at Week 133 (n= 2, 0)	-3.0000 (± 4.2426)	99999 (± 99999)		
PCS: Change at Week 145 (n= 1, 0)	-5.0000 (± 99999)	99999 (± 99999)		
PCS: Change at Week 157 (n= 1, 0)	0.0000 (± 99999)	99999 (± 99999)		
PCS: Change at Week 169 (n= 1, 0)	-3.0000 (± 99999)	99999 (± 99999)		
PCS: Change at Week 181 (n= 1, 0)	-2.0000 (± 99999)	99999 (± 99999)		
SWB: Baseline (n= 124, 133)	0.0000 (± 0.0000)	0.0000 (± 0.0000)		
SWB: Change at Week 1 (n= 106, 115)	0.0000 (± 0.0000)	0.0000 (± 0.0000)		
SWB: Change at Week 13 (n= 90, 100)	-0.1581 (± 4.1893)	-0.2953 (± 5.0738)		
SWB: Change at Week 25 (n= 62, 65)	-0.3634 (± 5.6959)	-0.0462 (± 3.7933)		
SWB: Change at Week 37 (n= 56, 45)	0.8798 (± 4.6897)	-0.3963 (± 3.3279)		
SWB: Change at Week 49 (n= 38, 23)	-0.0719 (± 6.2561)	-0.7536 (± 4.3164)		
SWB: Change at Week 61 (n= 18, 6)	-0.8167 (± 3.3323)	0.8333 (± 5.7067)		
SWB: Change at Week 73 (n= 11, 1)	-0.8182 (± 2.7863)	-24.0000 (± 99999)		
SWB: Change at Week 85 (n= 5, 1)	-3.6000 (± 3.7815)	-24.0000 (± 99999)		
SWB: Change at Week 97 (n= 4, 0)	-2.7500 (± 5.8523)	99999 (± 99999)		
SWB: Change at Week 109 (n= 3, 0)	-2.0000 (± 4.3589)	99999 (± 99999)		
SWB: Change at Week 121 (n= 2, 0)	0.5000 (± 0.7071)	99999 (± 99999)		
SWB: Change at Week 133 (n= 2, 0)	-1.0000 (± 1.4142)	99999 (± 99999)		
SWB: Change at Week 145 (n= 1, 0)	-2.0000 (± 99999)	99999 (± 99999)		
SWB: Change at Week 157 (n= 1, 0)	-3.0000 (± 99999)	99999 (± 99999)		
SWB: Change at Week 169 (n= 1, 0)	-3.0000 (± 99999)	99999 (± 99999)		
SWB: Change at Week 181 (n= 1, 0)	-2.0000 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQOL 5-dimension 5-level Questionnaire [EQ-5D-5L] Visual Analog Scale (VAS)

End point title	Change From Baseline in EuroQOL 5-dimension 5-level Questionnaire [EQ-5D-5L] Visual Analog Scale (VAS)
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End point description:

EQ-5D-5L is a health status instrument for self-reported assessment of 5 domains of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is rated by selecting 1

of 5 standardized categorizations ranging from no problem to extreme problem. The final question is a visual analogue scale (VAS) to rank health status from 0 (best health imaginable) to 100 (worst health imaginable). Participants in the FAS population with available data were analyzed. "99999"= No participants/only 1 participant was analyzed for the specified timepoint.

End point type	Secondary
End point timeframe:	
Period 2: Baseline, weeks 1, 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, 133, 145, 157, 169, 181	

End point values	Enzalutamide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	130		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 121, 130)	0.0 (± 0.0)	0.0 (± 0.0)		
Change at Week 1 (n= 106,113)	0.0 (± 0.0)	0.0 (± 0.0)		
Change at Week 13 (n= 89, 100)	2.3 (± 19.7)	-0.8 (± 17.8)		
Change at Week 25 (n= 63, 64)	-3.0 (± 18.6)	-0.2 (± 17.7)		
Change at Week 37 (n= 55, 47)	-1.3 (± 21.7)	0.4 (± 15.8)		
Change at Week 49 (n= 42, 24)	-2.5 (± 25.7)	-8.3 (± 23.3)		
Change at Week 61 (n= 19, 6)	1.3 (± 22.6)	2.5 (± 25.2)		
Change at Week 73 (n= 11, 1)	-3.5 (± 30.8)	-20.0 (± 99999)		
Change at Week 85 (n= 5, 1)	7.2 (± 20.7)	-10.0 (± 99999)		
Change at Week 97 (n= 4, 0)	17.8 (± 27.0)	99999 (± 99999)		
Change at Week 109 (n= 3, 0)	17.7 (± 23.6)	99999 (± 99999)		
Change at Week 121 (n= 2, 0)	-7.0 (± 4.2)	99999 (± 99999)		
Change at Week 133 (n= 2, 0)	0.5 (± 13.4)	99999 (± 99999)		
Change at Week 145 (n= 1, 0)	1.0 (± 99999)	99999 (± 99999)		
Change at Week 157 (n= 1, 0)	-4.0 (± 99999)	99999 (± 99999)		
Change at Week 169 (n= 1, 0)	2.0 (± 99999)	99999 (± 99999)		
Change at Week 181 (n= 1, 0)	-4.0 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose up to 30 days after last dose (median duration: 35 weeks)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	v23
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Reporting groups

Reporting group title	Period 1: Enzalutamide
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Reporting group description:

Participants received an OL treatment with enzalutamide 160 mg capsules, orally once daily from day 1 in period 1 until randomization to period 2 treatment, confirmation of ineligibility for period 2 treatment, intolerable toxicity, withdrawal, or death, whichever occurred first.

Reporting group title	Period 2: Placebo
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Reporting group description:

Participants with confirmed disease progression on enzalutamide in period 1 and who continued to meet all eligibility criteria received placebo matched to enzalutamide, orally once daily in combination with docetaxel 75 mg/m² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, in DB treatment period 2. Docetaxel and prednisolone were administered up to 10 cycles (1 cycle= 3 weeks) or additional cycles as assessed by the investigator and enzalutamide was administered until disease progression, intolerable toxicity, withdrawal or death, whichever occurred first.

Reporting group title	Period 2: Enzalutamide
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Reporting group description:

Participants with confirmed disease progression on enzalutamide in period 1 and who continued to meet all eligibility criteria received enzalutamide 160 mg capsules, orally once daily in combination with docetaxel 75 mg/m² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, DB treatment in period 2. Docetaxel and prednisolone were administered up to 10 cycles (1 cycle= 3 weeks) or additional cycles as assessed by the investigator and enzalutamide was administered until disease progression, intolerable toxicity, withdrawal or death, whichever occurred first.

Serious adverse events	Period 1: Enzalutamide	Period 2: Placebo	Period 2: Enzalutamide
Total subjects affected by serious adverse events			
subjects affected / exposed	235 / 687 (34.21%)	52 / 135 (38.52%)	67 / 136 (49.26%)
number of deaths (all causes)	50	14	18
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Bowen's disease			
subjects affected / exposed	1 / 687 (0.15%)	1 / 135 (0.74%)	0 / 136 (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
Bladder transitional cell carcinoma recurrent			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	4 / 687 (0.58%)	1 / 135 (0.74%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal adenocarcinoma			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Gastric cancer			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Colon cancer			

subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Lip neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Liposarcoma			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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 adenocarcinoma			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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 / 687 (0.15%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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 pleura			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Malignant neoplasm progression			
subjects affected / exposed	23 / 687 (3.35%)	6 / 135 (4.44%)	6 / 136 (4.41%)
occurrences causally related to treatment / all	0 / 25	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 14	0 / 3	0 / 5
Malignant peritoneal neoplasm			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Myeloproliferative neoplasm			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Pancreatic carcinoma			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Plasma cell myeloma			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Soft tissue sarcoma			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Transitional cell carcinoma			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Circulatory collapse			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Arterial insufficiency			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Haematoma			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Hypertension			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Hypotension			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant hypertension			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Shock haemorrhagic			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thrombosis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Venous thrombosis limb			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Bone operation			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Cardiac pacemaker removal			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Carpal tunnel decompression			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Catheterisation venous			

subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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			
Chest pain			
subjects affected / exposed	4 / 687 (0.58%)	1 / 135 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Fatigue			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	4 / 687 (0.58%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 4	0 / 0	0 / 1
Gait disturbance			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Generalised oedema			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	5 / 687 (0.73%)	3 / 135 (2.22%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 6	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Hypothermia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Pyrexia			
subjects affected / exposed	2 / 687 (0.29%)	2 / 135 (1.48%)	6 / 136 (4.41%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	5 / 687 (0.73%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Prostatitis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Scrotal pain			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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			
Cough			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Dyspnoea			
subjects affected / exposed	8 / 687 (1.16%)	1 / 135 (0.74%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	1 / 9	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrothorax			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Interstitial lung disease			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Pneumonitis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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 embolism			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Pulmonary thrombosis			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Hallucination			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Product issues			

Device dislocation			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis in device			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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	1 / 687 (0.15%)	1 / 135 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	5 / 687 (0.73%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 8	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 687 (0.15%)	1 / 135 (0.74%)	0 / 136 (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

Liver function test increased subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Neutrophil count decreased subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I increased subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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	8 / 687 (1.16%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	3 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Femoral neck fracture			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Femur fracture			
subjects affected / exposed	6 / 687 (0.87%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Hand fracture			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Infusion related reaction			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Medication error			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Overdose			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Procedural pain			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Product dispensing error			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Rib fracture			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Spinal fracture			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Tibia fracture			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Urostomy complication			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
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 disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Acute coronary syndrome			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Angina pectoris			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	12 / 687 (1.75%)	2 / 135 (1.48%)	3 / 136 (2.21%)
occurrences causally related to treatment / all	0 / 14	2 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Cardiac failure			
subjects affected / exposed	6 / 687 (0.87%)	1 / 135 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Congestive cardiomyopathy			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Coronary artery disease			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Dressler's syndrome			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Myocardial infarction			
subjects affected / exposed	8 / 687 (1.16%)	0 / 135 (0.00%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	1 / 9	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 1
Left ventricular failure			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Stress cardiomyopathy			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Palpitations			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amyotrophic lateral sclerosis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain compression			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Ataxia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Aphasia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Cerebrovascular accident			
subjects affected / exposed	4 / 687 (0.58%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Dementia Alzheimer's type			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Dizziness			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Headache			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hypertensive encephalopathy			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Hemiplegia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Ischaemic stroke			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			

subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Motor dysfunction			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraplegia			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Presyncope			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Sciatica			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Polyneuropathy			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Seizure			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Syncope			
subjects affected / exposed	5 / 687 (0.73%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	6 / 687 (0.87%)	1 / 135 (0.74%)	5 / 136 (3.68%)
occurrences causally related to treatment / all	1 / 6	0 / 1	0 / 5
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Vascular dementia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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	9 / 687 (1.31%)	2 / 135 (1.48%)	3 / 136 (2.21%)
occurrences causally related to treatment / all	6 / 17	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 687 (0.15%)	15 / 135 (11.11%)	10 / 136 (7.35%)
occurrences causally related to treatment / all	0 / 1	3 / 17	1 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Leukopenia			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	0 / 687 (0.00%)	5 / 135 (3.70%)	11 / 136 (8.09%)
occurrences causally related to treatment / all	0 / 0	1 / 12	1 / 21
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 687 (0.15%)	1 / 135 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Exfoliation glaucoma			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Blindness			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Vision blurred			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 687 (0.29%)	1 / 135 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 687 (0.15%)	1 / 135 (0.74%)	0 / 136 (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
Ascites			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Constipation			
subjects affected / exposed	2 / 687 (0.29%)	2 / 135 (1.48%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 687 (0.15%)	3 / 135 (2.22%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Gastric haemorrhage			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	5 / 687 (0.73%)	1 / 135 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Inguinal hernia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Large intestine perforation			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Intestinal obstruction			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Intestinal ischaemia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Mechanical ileus			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Pancreatitis			

subjects affected / exposed	1 / 687 (0.15%)	1 / 135 (0.74%)	0 / 136 (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
Nausea			
subjects affected / exposed	1 / 687 (0.15%)	2 / 135 (1.48%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Rectal haemorrhage			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Vomiting			
subjects affected / exposed	2 / 687 (0.29%)	1 / 135 (0.74%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Cholelithiasis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Stevens-Johnson syndrome			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Bladder tamponade			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder outlet obstruction			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	7 / 687 (1.02%)	2 / 135 (1.48%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 8	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 0
Haematuria			
subjects affected / exposed	12 / 687 (1.75%)	1 / 135 (0.74%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 17	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hydronephrosis			
subjects affected / exposed	6 / 687 (0.87%)	1 / 135 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral obstruction			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Urethral stenosis			

subjects affected / exposed	1 / 687 (0.15%)	1 / 135 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	7 / 687 (1.02%)	1 / 135 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary bladder polyp			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract disorder			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	3 / 687 (0.44%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Back pain			
subjects affected / exposed	12 / 687 (1.75%)	3 / 135 (2.22%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	1 / 14	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bone pain			
subjects affected / exposed	2 / 687 (0.29%)	1 / 135 (0.74%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Intervertebral disc disorder			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Flank pain			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Mobility decreased			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Muscular weakness			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Musculoskeletal chest pain			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Myalgia			

subjects affected / exposed	1 / 687 (0.15%)	1 / 135 (0.74%)	0 / 136 (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
Musculoskeletal pain			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Osteoarthritis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Osteonecrosis of jaw			
subjects affected / exposed	2 / 687 (0.29%)	1 / 135 (0.74%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	5 / 687 (0.73%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Infections and infestations			
Bronchitis bacterial			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Catheter bacteraemia			

subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Cellulitis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Dacryocystitis			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Diverticulitis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Erysipelas			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Infection			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lyme disease			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Infective aneurysm			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Meningitis bacterial			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Neutropenic sepsis			
subjects affected / exposed	1 / 687 (0.15%)	3 / 135 (2.22%)	5 / 136 (3.68%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	4 / 687 (0.58%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 687 (0.58%)	3 / 135 (2.22%)	4 / 136 (2.94%)
occurrences causally related to treatment / all	1 / 4	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary tuberculosis			

subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection fungal			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Sepsis			
subjects affected / exposed	5 / 687 (0.73%)	0 / 135 (0.00%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 5	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 687 (0.00%)	0 / 135 (0.00%)	3 / 136 (2.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Streptococcal urinary tract infection			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	0 / 136 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 687 (0.29%)	1 / 135 (0.74%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			

subjects affected / exposed	1 / 687 (0.15%)	1 / 135 (0.74%)	0 / 136 (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
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Urosepsis			
subjects affected / exposed	6 / 687 (0.87%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Dehydration			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Hyperglycaemia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Hypercalcaemia			
subjects affected / exposed	2 / 687 (0.29%)	0 / 135 (0.00%)	0 / 136 (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
Diabetes mellitus			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Hypocalcaemia			

subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Hypoglycaemia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (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
Hyponatraemia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Period 1: Enzalutamide	Period 2: Placebo	Period 2: Enzalutamide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	521 / 687 (75.84%)	123 / 135 (91.11%)	125 / 136 (91.91%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	22 / 687 (3.20%)	11 / 135 (8.15%)	8 / 136 (5.88%)
occurrences (all)	25	14	12
Vascular disorders			
Hot flush			
subjects affected / exposed	73 / 687 (10.63%)	1 / 135 (0.74%)	1 / 136 (0.74%)
occurrences (all)	89	1	1
Hypertension			

subjects affected / exposed occurrences (all)	90 / 687 (13.10%) 102	2 / 135 (1.48%) 2	3 / 136 (2.21%) 5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	109 / 687 (15.87%)	35 / 135 (25.93%)	46 / 136 (33.82%)
occurrences (all)	175	64	92
Pyrexia			
subjects affected / exposed	17 / 687 (2.47%)	7 / 135 (5.19%)	9 / 136 (6.62%)
occurrences (all)	18	9	11
Oedema peripheral			
subjects affected / exposed	26 / 687 (3.78%)	20 / 135 (14.81%)	16 / 136 (11.76%)
occurrences (all)	31	23	18
Mucosal inflammation			
subjects affected / exposed	3 / 687 (0.44%)	17 / 135 (12.59%)	10 / 136 (7.35%)
occurrences (all)	3	19	14
Fatigue			
subjects affected / exposed	158 / 687 (23.00%)	28 / 135 (20.74%)	40 / 136 (29.41%)
occurrences (all)	193	41	65
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 687 (3.78%)	10 / 135 (7.41%)	11 / 136 (8.09%)
occurrences (all)	30	11	15
Dyspnoea			
subjects affected / exposed	28 / 687 (4.08%)	4 / 135 (2.96%)	11 / 136 (8.09%)
occurrences (all)	31	4	13
Epistaxis			
subjects affected / exposed	10 / 687 (1.46%)	7 / 135 (5.19%)	13 / 136 (9.56%)
occurrences (all)	11	9	16
Investigations			
Weight decreased			
subjects affected / exposed	30 / 687 (4.37%)	2 / 135 (1.48%)	11 / 136 (8.09%)
occurrences (all)	36	2	11
Neutrophil count decreased			
subjects affected / exposed	3 / 687 (0.44%)	7 / 135 (5.19%)	7 / 136 (5.15%)
occurrences (all)	4	27	14
Haemoglobin decreased			

subjects affected / exposed occurrences (all)	15 / 687 (2.18%) 17	7 / 135 (5.19%) 7	2 / 136 (1.47%) 3
White blood cell count decreased subjects affected / exposed occurrences (all)	9 / 687 (1.31%) 12	7 / 135 (5.19%) 24	5 / 136 (3.68%) 17
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	45 / 687 (6.55%) 61	4 / 135 (2.96%) 4	6 / 136 (4.41%) 7
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	10 / 687 (1.46%) 12	9 / 135 (6.67%) 9	18 / 136 (13.24%) 22
Dizziness subjects affected / exposed occurrences (all)	45 / 687 (6.55%) 49	6 / 135 (4.44%) 6	5 / 136 (3.68%) 5
Headache subjects affected / exposed occurrences (all)	44 / 687 (6.40%) 56	8 / 135 (5.93%) 10	5 / 136 (3.68%) 6
Neuropathy peripheral subjects affected / exposed occurrences (all)	2 / 687 (0.29%) 2	12 / 135 (8.89%) 21	22 / 136 (16.18%) 29
Taste disorder subjects affected / exposed occurrences (all)	7 / 687 (1.02%) 7	9 / 135 (6.67%) 11	6 / 136 (4.41%) 6
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 687 (0.15%) 1	14 / 135 (10.37%) 25	12 / 136 (8.82%) 16
Paraesthesia subjects affected / exposed occurrences (all)	22 / 687 (3.20%) 24	10 / 135 (7.41%) 21	8 / 136 (5.88%) 10
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	5 / 687 (0.73%) 5	43 / 135 (31.85%) 129	41 / 136 (30.15%) 124
Anaemia			

subjects affected / exposed occurrences (all)	49 / 687 (7.13%) 63	15 / 135 (11.11%) 32	27 / 136 (19.85%) 47
Leukopenia subjects affected / exposed occurrences (all)	1 / 687 (0.15%) 1	16 / 135 (11.85%) 48	11 / 136 (8.09%) 37
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	2 / 687 (0.29%) 3	6 / 135 (4.44%) 7	25 / 136 (18.38%) 28
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	60 / 687 (8.73%) 64	15 / 135 (11.11%) 17	12 / 136 (8.82%) 21
Diarrhoea subjects affected / exposed occurrences (all)	63 / 687 (9.17%) 76	42 / 135 (31.11%) 67	37 / 136 (27.21%) 51
Nausea subjects affected / exposed occurrences (all)	69 / 687 (10.04%) 79	25 / 135 (18.52%) 31	26 / 136 (19.12%) 33
Stomatitis subjects affected / exposed occurrences (all)	2 / 687 (0.29%) 2	8 / 135 (5.93%) 9	5 / 136 (3.68%) 5
Vomiting subjects affected / exposed occurrences (all)	22 / 687 (3.20%) 25	6 / 135 (4.44%) 6	8 / 136 (5.88%) 8
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	2 / 687 (0.29%) 2	37 / 135 (27.41%) 48	44 / 136 (32.35%) 56
Dry skin subjects affected / exposed occurrences (all)	14 / 687 (2.04%) 14	5 / 135 (3.70%) 5	12 / 136 (8.82%) 12
Nail disorder subjects affected / exposed occurrences (all)	0 / 687 (0.00%) 0	7 / 135 (5.19%) 8	13 / 136 (9.56%) 13
Nail dystrophy			

subjects affected / exposed	0 / 687 (0.00%)	2 / 135 (1.48%)	7 / 136 (5.15%)
occurrences (all)	0	3	9
Nail toxicity			
subjects affected / exposed	0 / 687 (0.00%)	5 / 135 (3.70%)	11 / 136 (8.09%)
occurrences (all)	0	7	16
Onycholysis			
subjects affected / exposed	0 / 687 (0.00%)	12 / 135 (8.89%)	13 / 136 (9.56%)
occurrences (all)	0	16	14
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	0 / 687 (0.00%)	1 / 135 (0.74%)	10 / 136 (7.35%)
occurrences (all)	0	1	15
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	39 / 687 (5.68%)	7 / 135 (5.19%)	4 / 136 (2.94%)
occurrences (all)	48	8	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	116 / 687 (16.89%)	14 / 135 (10.37%)	13 / 136 (9.56%)
occurrences (all)	152	15	15
Arthralgia			
subjects affected / exposed	70 / 687 (10.19%)	10 / 135 (7.41%)	25 / 136 (18.38%)
occurrences (all)	85	10	27
Bone pain			
subjects affected / exposed	64 / 687 (9.32%)	14 / 135 (10.37%)	12 / 136 (8.82%)
occurrences (all)	79	16	14
Myalgia			
subjects affected / exposed	22 / 687 (3.20%)	7 / 135 (5.19%)	9 / 136 (6.62%)
occurrences (all)	23	9	9
Musculoskeletal pain			
subjects affected / exposed	32 / 687 (4.66%)	7 / 135 (5.19%)	5 / 136 (3.68%)
occurrences (all)	37	12	7
Pain in extremity			
subjects affected / exposed	43 / 687 (6.26%)	7 / 135 (5.19%)	7 / 136 (5.15%)
occurrences (all)	54	7	10
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	28 / 687 (4.08%) 33	8 / 135 (5.93%) 8	4 / 136 (2.94%) 5
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	69 / 687 (10.04%) 86	17 / 135 (12.59%) 18	23 / 136 (16.91%) 28

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2014	<p>The changes included:</p> <ul style="list-style-type: none">• Extended the contraception/sperm donation requirements in period 2 from 3 months after last IMP to 6 months after last dose of docetaxel.• Reduced threshold for excluding patients based on elevated bilirubin levels in periods 1 and 2. Introduced additional biochemistry testing of patients with elevated liver function tests (LFTs) in period 2 prior to each docetaxel cycle.• Removed docetaxel brand name and allowed local provision of docetaxel.• Deleted requirement that site contact sponsor to assess necessity of breaking blind.
19 June 2015	<p>The changes included:</p> <ul style="list-style-type: none">• Added the collection of blood samples to analyze candidate biomarkers in circulation for association with response or progression and for identifying mechanisms of resistance.• Clarified that any patients who were enrolled in a noninterventional control arm of an interventional study could be enrolled, provided they met all other inclusion and exclusion criteria.
13 June 2016	<p>The changes included:</p> <ul style="list-style-type: none">• Added an extension period to period 1 to allow treatment continuation for patients still in period 1 after enrollment to period 2 is completed. Added an extension period to period 2 to allow treatment continuation for patients still in period 2 after the cutoff for data analysis was reached.• Removed the per protocol set.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported