



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	13 March 2024

Results information

Result version number	v2
This version publication date	07 December 2024
First version publication date	15 October 2021
Version creation reason	

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), +44 (0) 20 3379 8000, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe Ltd. (APEL), +44 (0) 20 3379 8000, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 March 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to 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	Türkiye: 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: 462 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 OL enzalutamide 160 milligrams (mg) capsules orally once daily (QD) from Day 1 in Period (P) 1 until they were either randomized to P2 treatment, deemed ineligible, experienced intolerable toxicity, withdrew, or died, whichever came first. An Extension (EXT) phase was available for participants still in P1 not meeting the primary endpoint, when the data cut-off for analysis was reached. Treatment with enzalutamide continued until the disease progression, intolerable toxicity, participant withdrawal or death. Participants who did not enter EXT phase had discontinued study and received local standard of care treatment. Those who were still benefiting from enzalutamide treatment in EXT phase at study closure continued enzalutamide therapy in another Astellas-sponsored study 9785-CL-0123 or via commercially available enzalutamide.

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	0
Not completed	688
Study Terminated By Sponsor	2
Death	35
Progressive Disease	393

Not specified	142
Adverse event	52
Withdrawal by Subject	54
Lost to follow-up	1
Protocol deviation	9

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?	No
Arm title	Period 2: Enzalutamide

Arm description:

Participants with confirmed disease progression on enzalutamide in P1, who continued to meet eligibility criteria, received enzalutamide 160 mg orally QD, in combination with docetaxel 75 milligrams per meter square (mg/m²) via a 1-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily in P2. Docetaxel and prednisolone were administered for up to 10 cycles (1 cycle = 3 weeks) or as determined by the investigator. Enzalutamide continued until disease progression, intolerable toxicity, withdrawal, or death. An EXT phase was available for participants not meeting the primary endpoint at the data cut-off. Those who didn't enter EXT phase received local standard care, while others continued enzalutamide in another Astellas study 9785-CL-0123 or via commercially available enzalutamide.

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
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Arm description:

Participants with confirmed disease progression on enzalutamide in P1 and who continued to meet all eligibility criteria received placebo matched to enzalutamide, orally QD in combination with docetaxel 75 mg/m² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, DB in P2. 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.

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	Period 2: Enzalutamide	Period 2: Placebo
Started	137	136
Treated	136	135
Completed	0	1
Not completed	137	135
Randomized but not treated	1	-
Death	8	4
Progressive Disease	87	94
Not specified	21	21
Adverse event	10	8
Withdrawal by Subject	7	7
Lost to follow-up	1	-
Protocol deviation	2	1

Baseline characteristics

Reporting groups

Reporting group title	Period 1: OL Treatment (Max: 462 weeks)
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Reporting group description: -

Reporting group values	Period 1: OL Treatment (Max: 462 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
Reporting group description:	
Participants received OL enzalutamide 160 milligrams (mg) capsules orally once daily (QD) from Day 1 in Period (P) 1 until they were either randomized to P2 treatment, deemed ineligible, experienced intolerable toxicity, withdrew, or died, whichever came first. An Extension (EXT) phase was available for participants still in P1 not meeting the primary endpoint, when the data cut-off for analysis was reached. Treatment with enzalutamide continued until the disease progression, intolerable toxicity, participant withdrawal or death. Participants who did not enter EXT phase had discontinued study and received local standard of care treatment. Those who were still benefiting from enzalutamide treatment in EXT phase at study closure continued enzalutamide therapy in another Astellas-sponsored study 9785-CL-0123 or via commercially available enzalutamide.	
Reporting group title	Period 2: Enzalutamide
Reporting group description:	
Participants with confirmed disease progression on enzalutamide in P1, who continued to meet eligibility criteria, received enzalutamide 160 mg orally QD, in combination with docetaxel 75 milligrams per meter square (mg/m ²) via a 1-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily in P2. Docetaxel and prednisolone were administered for up to 10 cycles (1 cycle = 3 weeks) or as determined by the investigator. Enzalutamide continued until disease progression, intolerable toxicity, withdrawal, or death. An EXT phase was available for participants not meeting the primary endpoint at the data cut-off. Those who didn't enter EXT phase received local standard care, while others continued enzalutamide in another Astellas study 9785-CL-0123 or via commercially available enzalutamide.	
Reporting group title	Period 2: Placebo
Reporting group description:	
Participants with confirmed disease progression on enzalutamide in P1 and who continued to meet all eligibility criteria received placebo matched to enzalutamide, orally QD in combination with docetaxel 75 mg/m ² in a one-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily, DB in P2. 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.	
Subject analysis set title	Enzalutamide
Subject analysis set type	Full analysis
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/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.	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
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/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.	

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	135		
Units: months				
median (confidence interval 95%)	9.53 (8.25 to 10.87)	8.28 (6.28 to 8.71)		

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 ^[1]
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:

[1] - 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
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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: Time to Prostate-specific Antigen (PSA) progression

End point title	Time to Prostate-specific Antigen (PSA) progression
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 ^[2]
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:

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

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 ^[3]
Method	Cochran-Mantel-Haenszel

Notes:

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

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

End point title	Time to first Skeletal-related Event (SRE)
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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
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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%)	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 ^[4]
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:

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

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	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 opiate use for cancer-related pain

End point title	Time to opiate use for cancer-related pain
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
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: 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)
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=Somewhat, 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
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 (± 9999999999)	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
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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	136	135		
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 71 weeks

Adverse event reporting additional description:

Safety Analysis Set 1 (SAF1) consists of all participants who took at least one dose of study drug during Period 1. Safety Analysis Set 2 (SAF2) consists of all participants who took at least one dose of study drug during Period 2.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	v23.0
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Reporting groups

Reporting group title	Period 1: Enzalutamide
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Reporting group description:

Participants received OL enzalutamide 160 mg capsules orally QD from P1 until they were either randomized to P2 treatment, deemed ineligible, experienced intolerable toxicity, withdrew, or died, whichever came first. An EXT phase was available for participants still in P1 not meeting the primary endpoint, when the data cut-off for analysis was reached. Treatment with enzalutamide continued until the disease progression, intolerable toxicity, participant withdrawal or death. Participants who did not enter EXT phase had discontinued study and received local standard of care treatment. Those who were still benefiting from enzalutamide treatment in EXT phase at study closure continued enzalutamide therapy in another Astellas-sponsored study 9785-CL-0123 or via commercially available enzalutamide.

Reporting group title	Period 2: Placebo
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Reporting group description:

Participants with confirmed disease progression on enzalutamide in P1 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, DB in P2. 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 P1, who continued to meet eligibility criteria, received enzalutamide 160 mg orally once daily, in combination with docetaxel 75 mg/m² via a 1-hour infusion every 3 weeks and prednisolone 5 mg orally twice daily in period 2. Docetaxel and prednisolone were administered for up to 10 cycles (1 cycle = 3 weeks) or as determined by the investigator. Enzalutamide continued until disease progression, intolerable toxicity, withdrawal, or death. An EXT phase was available for participants not meeting the primary endpoint at the data cut-off. Those who didn't enter EXT received local standard care, while others continued enzalutamide in another Astellas study 9785-CL-0123 or via commercially available enzalutamide.

Serious adverse events	Period 1: Enzalutamide	Period 2: Placebo	Period 2: Enzalutamide
Total subjects affected by serious adverse events			
subjects affected / exposed	238 / 687 (34.64%)	52 / 135 (38.52%)	67 / 136 (49.26%)
number of deaths (all causes)	51	15	18
number of deaths resulting from adverse events	45	7	13
Neoplasms benign, malignant and unspecified (incl cysts and polyps) 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
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
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
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
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
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
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
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
Malignant neoplasm progression			
subjects affected / exposed	22 / 687 (3.20%)	6 / 135 (4.44%)	6 / 136 (4.41%)
occurrences causally related to treatment / all	0 / 24	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 13	0 / 3	0 / 5
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
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
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
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
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
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
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
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
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
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
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
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
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
Transitional cell carcinoma			
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
Uveal melanoma			
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			
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
Respiratory, thoracic and mediastinal disorders			
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
Dyspnoea			
subjects affected / exposed	8 / 687 (1.16%)	1 / 135 (0.74%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	1 / 11	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
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
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

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
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 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
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
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
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
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
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			

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
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
Product issues			
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
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
Investigations			
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
Incorrect dose administered			
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
Urinary tract stoma complication			
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 disorders			
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
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
Angina pectoris			
subjects affected / exposed	4 / 687 (0.58%)	0 / 135 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	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
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
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
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
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
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
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
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
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	9 / 687 (1.31%)	0 / 135 (0.00%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	1 / 10	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 1
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
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
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
Nervous system disorders			
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
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
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
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
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
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
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
Cerebrovascular accident			
subjects affected / exposed	5 / 687 (0.73%)	0 / 135 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
Dyspepsia			
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
Hepatobiliary disorders			
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
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
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			
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
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

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 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
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
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
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
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
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
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
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			
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
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
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

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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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	5 / 687 (0.73%)	3 / 135 (2.22%)	4 / 136 (2.94%)
occurrences causally related to treatment / all	1 / 5	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
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
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
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
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
COVID-19 pneumonia			

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
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
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
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
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
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
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
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
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
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

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	523 / 687 (76.13%)	123 / 135 (91.11%)	125 / 136 (91.91%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	23 / 687 (3.35%)	11 / 135 (8.15%)	8 / 136 (5.88%)
occurrences (all)	26	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	91 / 687 (13.25%)	2 / 135 (1.48%)	3 / 136 (2.21%)
occurrences (all)	103	2	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	94
Oedema peripheral			

subjects affected / exposed occurrences (all)	26 / 687 (3.78%) 31	20 / 135 (14.81%) 23	16 / 136 (11.76%) 18
Fatigue subjects affected / exposed occurrences (all)	159 / 687 (23.14%) 194	28 / 135 (20.74%) 41	40 / 136 (29.41%) 65
Mucosal inflammation subjects affected / exposed occurrences (all)	3 / 687 (0.44%) 3	17 / 135 (12.59%) 19	10 / 136 (7.35%) 14
Pyrexia subjects affected / exposed occurrences (all)	18 / 687 (2.62%) 19	7 / 135 (5.19%) 9	9 / 136 (6.62%) 11
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed occurrences (all)	10 / 687 (1.46%) 11	7 / 135 (5.19%) 9	13 / 136 (9.56%) 16
Dyspnoea subjects affected / exposed occurrences (all)	28 / 687 (4.08%) 30	4 / 135 (2.96%) 4	11 / 136 (8.09%) 13
Cough subjects affected / exposed occurrences (all)	27 / 687 (3.93%) 32	10 / 135 (7.41%) 11	11 / 136 (8.09%) 15
Investigations			
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
Weight decreased subjects affected / exposed occurrences (all)	30 / 687 (4.37%) 36	2 / 135 (1.48%) 2	11 / 136 (8.09%) 11
Neutrophil count decreased subjects affected / exposed occurrences (all)	3 / 687 (0.44%) 4	7 / 135 (5.19%) 27	7 / 136 (5.15%) 14
Haemoglobin decreased subjects affected / exposed occurrences (all)	15 / 687 (2.18%) 17	7 / 135 (5.19%) 7	2 / 136 (1.47%) 3
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	47 / 687 (6.84%)	4 / 135 (2.96%)	6 / 136 (4.41%)
occurrences (all)	64	4	7
Nervous system disorders			
Taste disorder			
subjects affected / exposed	7 / 687 (1.02%)	9 / 135 (6.67%)	6 / 136 (4.41%)
occurrences (all)	7	11	6
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 687 (0.15%)	14 / 135 (10.37%)	12 / 136 (8.82%)
occurrences (all)	1	25	16
Paraesthesia			
subjects affected / exposed	22 / 687 (3.20%)	10 / 135 (7.41%)	8 / 136 (5.88%)
occurrences (all)	24	21	10
Neuropathy peripheral			
subjects affected / exposed	2 / 687 (0.29%)	12 / 135 (8.89%)	22 / 136 (16.18%)
occurrences (all)	2	21	29
Headache			
subjects affected / exposed	44 / 687 (6.40%)	8 / 135 (5.93%)	5 / 136 (3.68%)
occurrences (all)	56	10	6
Dysgeusia			
subjects affected / exposed	10 / 687 (1.46%)	9 / 135 (6.67%)	18 / 136 (13.24%)
occurrences (all)	12	9	22
Dizziness			
subjects affected / exposed	45 / 687 (6.55%)	6 / 135 (4.44%)	5 / 136 (3.68%)
occurrences (all)	49	6	5
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	5 / 687 (0.73%)	43 / 135 (31.85%)	41 / 136 (30.15%)
occurrences (all)	5	129	125
Leukopenia			
subjects affected / exposed	1 / 687 (0.15%)	16 / 135 (11.85%)	11 / 136 (8.09%)
occurrences (all)	1	48	37
Anaemia			
subjects affected / exposed	49 / 687 (7.13%)	15 / 135 (11.11%)	27 / 136 (19.85%)
occurrences (all)	63	32	47
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			
Vomiting subjects affected / exposed occurrences (all)	22 / 687 (3.20%) 25	6 / 135 (4.44%) 6	8 / 136 (5.88%) 8
Stomatitis subjects affected / exposed occurrences (all)	2 / 687 (0.29%) 2	8 / 135 (5.93%) 9	5 / 136 (3.68%) 5
Nausea subjects affected / exposed occurrences (all)	69 / 687 (10.04%) 79	25 / 135 (18.52%) 31	26 / 136 (19.12%) 33
Diarrhoea subjects affected / exposed occurrences (all)	63 / 687 (9.17%) 77	42 / 135 (31.11%) 67	37 / 136 (27.21%) 51
Constipation subjects affected / exposed occurrences (all)	60 / 687 (8.73%) 64	15 / 135 (11.11%) 17	12 / 136 (8.82%) 21
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	0 / 687 (0.00%) 0	1 / 135 (0.74%) 1	10 / 136 (7.35%) 15
Onycholysis subjects affected / exposed occurrences (all)	0 / 687 (0.00%) 0	12 / 135 (8.89%) 16	13 / 136 (9.56%) 14
Nail toxicity subjects affected / exposed occurrences (all)	0 / 687 (0.00%) 0	5 / 135 (3.70%) 7	11 / 136 (8.09%) 16
Nail dystrophy subjects affected / exposed occurrences (all)	0 / 687 (0.00%) 0	2 / 135 (1.48%) 3	7 / 136 (5.15%) 9
Dry skin subjects affected / exposed occurrences (all)	14 / 687 (2.04%) 14	5 / 135 (3.70%) 5	12 / 136 (8.82%) 12
Alopecia			

subjects affected / exposed occurrences (all)	2 / 687 (0.29%) 2	37 / 135 (27.41%) 48	44 / 136 (32.35%) 56
Nail disorder subjects affected / exposed occurrences (all)	0 / 687 (0.00%) 0	7 / 135 (5.19%) 8	13 / 136 (9.56%) 13
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	41 / 687 (5.97%) 50	7 / 135 (5.19%) 8	4 / 136 (2.94%) 5
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	117 / 687 (17.03%) 153	14 / 135 (10.37%) 15	13 / 136 (9.56%) 15
Arthralgia subjects affected / exposed occurrences (all)	70 / 687 (10.19%) 85	10 / 135 (7.41%) 10	25 / 136 (18.38%) 27
Bone pain subjects affected / exposed occurrences (all)	64 / 687 (9.32%) 80	14 / 135 (10.37%) 16	12 / 136 (8.82%) 14
Pain in extremity subjects affected / exposed occurrences (all)	44 / 687 (6.40%) 55	7 / 135 (5.19%) 7	7 / 136 (5.15%) 10
Myalgia subjects affected / exposed occurrences (all)	22 / 687 (3.20%) 23	7 / 135 (5.19%) 9	9 / 136 (6.62%) 9
Musculoskeletal pain subjects affected / exposed occurrences (all)	33 / 687 (4.80%) 38	7 / 135 (5.19%) 12	5 / 136 (3.68%) 7
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	• The changes included extended the contraception/sperm donation requirements in period 2 from 3 months after last IMP to 6 months after last dose of docetaxel. • The changes included reduced threshold for excluding participants based on elevated bilirubin levels in periods 1 and 2. Introduced additional biochemistry testing of participants with elevated liver function tests (LFTs) in period 2 prior to each docetaxel cycle. • The changes included removed docetaxel brand name and allowed local provision of docetaxel. • The changes included deleted requirement that site contact sponsor to assess necessity of breaking blind.
19 June 2015	• The changes included added the collection of blood samples to analyze candidate biomarkers in circulation for association with response or progression and for identifying mechanisms of resistance. • The changes included clarified that any participants 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	• The changes included added an extension period to period 1 to allow treatment continuation for participants still in period 1 after enrollment to period 2 is completed. Added an extension period to period 2 to allow treatment continuation for participants still in period 2 after the cutoff for data analysis was reached. • The changes included removed the per protocol set.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported