

**Clinical trial results:****PROSPER: A Multinational, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer
Summary**

EudraCT number	2012-005665-12
Trial protocol	SE IT AT BE GB SK FI NL ES GR FR DK DE
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	31 October 2020
First version publication date	15 July 2018
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	C3431005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02003924
WHO universal trial number (UTN)	-
Other trial identifiers	MDV3100-14: Alias Study Number

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	15 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of enzalutamide compared with placebo as assessed by Metastasis-free survival (MFS).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 99
Country: Number of subjects enrolled	United States: 105
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Denmark: 83
Country: Number of subjects enrolled	Finland: 33
Country: Number of subjects enrolled	France: 103
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Greece: 42
Country: Number of subjects enrolled	Italy: 58
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Serbia: 13
Country: Number of subjects enrolled	Slovakia: 47
Country: Number of subjects enrolled	Spain: 47
Country: Number of subjects enrolled	Sweden: 30
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	Ukraine: 52
Country: Number of subjects enrolled	United Kingdom: 70

Country: Number of subjects enrolled	Argentina: 12
Country: Number of subjects enrolled	Australia: 136
Country: Number of subjects enrolled	Brazil: 104
Country: Number of subjects enrolled	Chile: 12
Country: Number of subjects enrolled	China: 79
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 54
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	New Zealand: 27
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Taiwan: 48
Country: Number of subjects enrolled	Thailand: 14
Worldwide total number of subjects	1401
EEA total number of subjects	588

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)	190
From 65 to 84 years	1108
85 years and over	103

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at 254 sites in 32 countries. Data reported based on primary analysis date (28 June 2017).

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Enzalutamide 160 mg

Arm description:

Subjects received 4 capsules of Enzalutamide 40 mg each (total dose 160 mg per day) orally, once daily in double-blind and open-label phase (up to a maximum of 68.8 months) until radiographic progression. Subjects after last dose of study drug, were followed up for safety up to 30 days, and were long term followed up (for survival status and new prostate cancer therapies) from last dose to the death date or last known survival date.

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

Dosage and administration details:

Four capsules of Enzalutamide 40 mg each (total dose 160 mg per day) orally, once daily.

Arm title	Placebo
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Arm description:

Subjects received 4 capsules of placebo (matched to Enzalutamide) orally, once daily in double blind phase (up to a maximum of 51.3 months) until radiographic progression. Subjects were given an opportunity to switch to open-label enzalutamide after completion of double blind phase. Subjects after last dose of study drug, were followed up for safety up to 30 days and were long term followed up (for survival status and new prostate cancer therapies) to the death date or last known survival date.

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

Dosage and administration details:

Four capsules of Placebo (matched to Enzalutamide) orally, once daily.

Arm title	Placebo Subjects Crossover to Enzalutamide 160 mg
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Arm description:

Subjects who received placebo in double-blind phase and who agreed to proceed to open-label phase, received 4 capsules of Enzalutamide 40 mg each (total dose of 160 mg per day), orally once daily (up to a maximum of 18.8 months) until radiographic progression. Subjects after last dose of study drug, were followed up for safety up to 30 days and were long term followed up (for survival status and new

prostate cancer therapies) to the death date or last known survival date.

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

Dosage and administration details:

Four capsules of Enzalutamide 40 mg each (total dose 160 mg per day) orally, once daily.

Number of subjects in period 1	Enzalutamide 160 mg	Placebo	Placebo Subjects Crossover to Enzalutamide 160 mg
Started	933	468	87
Treated in double blind phase	930	465	0 [1]
Completed in double-blind phase	478 [2]	87 [3]	0 [4]
Treated in open label phase	478 [5]	0 [6]	87
Completed in open label phase	378 [7]	0 [8]	70 [9]
Completed	566	231	80
Not completed	367	237	7
Withdrew Consent to Be Followed	66	55	1
Death	288	174	4
Unspecified	5	2	1
Lost to follow-up	8	6	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects in Enzalutamide 160 mg continued treatment in double blind and open-label phase. Subjects in placebo arm received treatment only in double blind phase and after protocol amendment they had an opportunity to receive open label Enzalutamide 160 mg. Subjects who discontinued treatment were followed up in long term phase.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects in Enzalutamide 160 mg continued treatment in double blind and open-label phase. Subjects in placebo arm received treatment only in double blind phase and after protocol amendment they had an opportunity to receive open label Enzalutamide 160 mg. Subjects who discontinued treatment were followed up in long term phase.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects in Enzalutamide 160 mg continued treatment in double blind and open-label phase. Subjects in placebo arm received treatment only in double blind phase and after protocol amendment they had an opportunity to receive open label Enzalutamide 160 mg. Subjects who discontinued treatment were followed up in long term phase.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects in Enzalutamide 160 mg continued treatment in double blind and open-label phase. Subjects in placebo arm received treatment only in double blind phase and after protocol

amendment they had an opportunity to receive open label Enzalutamide 160 mg. Subjects who discontinued treatment were followed up in long term phase.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects in Enzalutamide 160 mg continued treatment in double blind and open-label phase. Subjects in placebo arm received treatment only in double blind phase and after protocol amendment they had an opportunity to receive open label Enzalutamide 160 mg. Subjects who discontinued treatment were followed up in long term phase.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects in Enzalutamide 160 mg continued treatment in double blind and open-label phase. Subjects in placebo arm received treatment only in double blind phase and after protocol amendment they had an opportunity to receive open label Enzalutamide 160 mg. Subjects who discontinued treatment were followed up in long term phase.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects in Enzalutamide 160 mg continued treatment in double blind and open-label phase. Subjects in placebo arm received treatment only in double blind phase and after protocol amendment they had an opportunity to receive open label Enzalutamide 160 mg. Subjects who discontinued treatment were followed up in long term phase.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects in Enzalutamide 160 mg continued treatment in double blind and open-label phase. Subjects in placebo arm received treatment only in double blind phase and after protocol amendment they had an opportunity to receive open label Enzalutamide 160 mg. Subjects who discontinued treatment were followed up in long term phase.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects in Enzalutamide 160 mg continued treatment in double blind and open-label phase. Subjects in placebo arm received treatment only in double blind phase and after protocol amendment they had an opportunity to receive open label Enzalutamide 160 mg. Subjects who discontinued treatment were followed up in long term phase.

Baseline characteristics

Reporting groups

Reporting group title	Overall period
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Reporting group description:

All subjects those who were randomized.

Reporting group values	Overall period	Total	
Number of subjects	1401	1401	
Age categorical			
The intent-to-treat (ITT) population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered.			
Units: Subjects			
Adults (18-64 years)	190	190	
From 65-84 years	1108	1108	
85 years and over	103	103	
Age Continuous			
The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered.			
Units: years			
arithmetic mean	73.5		
standard deviation	± 7.77	-	
Sex: Female, Male			
The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered.			
Units: Subjects			
Female	0	0	
Male	1401	1401	
Race/Ethnicity, Customized			
The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered.			
Units: Subjects			
Asian	230	230	
Black or African American	31	31	
Native Hawaiian or Other Pacific Islander	5	5	
White	991	991	
Multiple	8	8	
Other	20	20	
Missing	116	116	

End points

End points reporting groups

Reporting group title	Enzalutamide 160 mg
Reporting group description: Subjects received 4 capsules of Enzalutamide 40 mg each (total dose 160 mg per day) orally, once daily in double-blind and open-label phase (up to a maximum of 68.8 months) until radiographic progression. Subjects after last dose of study drug, were followed up for safety up to 30 days, and were long term followed up (for survival status and new prostate cancer therapies) from last dose to the death date or last known survival date.	
Reporting group title	Placebo
Reporting group description: Subjects received 4 capsules of placebo (matched to Enzalutamide) orally, once daily in double blind phase (up to a maximum of 51.3 months) until radiographic progression. Subjects were given an opportunity to switch to open-label enzalutamide after completion of double blind phase. Subjects after last dose of study drug, were followed up for safety up to 30 days and were long term followed up (for survival status and new prostate cancer therapies) to the death date or last known survival date.	
Reporting group title	Placebo Subjects Crossover to Enzalutamide 160 mg
Reporting group description: Subjects who received placebo in double-blind phase and who agreed to proceed to open-label phase, received 4 capsules of Enzalutamide 40 mg each (total dose of 160 mg per day), orally once daily (up to a maximum of 18.8 months) until radiographic progression. Subjects after last dose of study drug, were followed up for safety up to 30 days and were long term followed up (for survival status and new prostate cancer therapies) to the death date or last known survival date.	

Primary: Metastasis Free Survival (MFS)

End point title	Metastasis Free Survival (MFS) ^[1]
End point description: MFS:time from randomization to first date of radiographic progression (RP) at any time or death within 112 days of treatment discontinuation without evidence of RP.RP for bone disease:appearance of 1 or more metastatic lesions on bone scan.RP for soft tissue disease:per RECIST,v1.1-at least 20% increase in the sum of diameters of target lesions,reference to smallest sum on study.Subjects who did not have MFS event at the time of analysis data cut-off (28 June 2017) were censored at date of last assessment showing no objective evidence of RP prior to skeletal-related event or two or more consecutive missed tumor assessments. Subjects randomized but later confirmed to have metastatic disease before randomization were censored on date of randomization.ITT population:subjects randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered.The upper limit of 95% CI was not reached and has been denoted as 99999.	
End point type	Primary
End point timeframe: From randomization until radiographic progression at any time, or death within 112 days of treatment discontinuation, whichever occurred first (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)	
Notes: [1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo	

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: months				
median (confidence interval 95%)	36.6 (33.1 to 99999)	14.7 (14.2 to 15.0)		

Statistical analyses

Statistical analysis title	Enzalutamide 160 mg Vs. Placebo
Comparison groups	Enzalutamide 160 mg v Placebo
Number of subjects included in analysis	1401
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.292
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.241
upper limit	0.352

Notes:

[2] - P-value was based on stratified log-rank test by prostate-specific antigen (PSA) doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone targeting agent (yes, no). Threshold for significance at 0.05 level.

Secondary: Time to Prostate-Specific Antigen (PSA) Progression

End point title	Time to Prostate-Specific Antigen (PSA) Progression ^[3]
End point description:	
Time to PSA progression: time from randomization to the date of first PSA value indicating progression, which was subsequently confirmed. For subjects with PSA decline at Week 17, PSA progression was defined according to PCWG2 guidelines as date that a 25% or greater increase and an absolute increase of 2 nanograms per milliliter (ng/mL) above the nadir (or baseline for subjects with no PSA decline by Week 17) was documented, which was confirmed by a second consecutive value obtained at least 3 weeks or later. Subjects without confirmed PSA progression at the time of analysis were right censored at the date of last PSA assessment before the analysis data cut-off date for the purposes of analysis. Analysis was based on Kaplan-Meier estimates. ITT population: all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. The upper limit of 95% CI was not reached and has been denoted as	
End point type	Secondary

End point timeframe:

From randomization until first PSA progression (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: months				
median (confidence interval 95%)	37.2 (33.1 to 99999)	3.9 (3.8 to 4.0)		

Statistical analyses

Statistical analysis title	Enzalutamide 160 mg Vs. Placebo
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Statistical analysis description:

To maintain the family-wise 2-sided type I error rate at 0.05, a parallel testing strategy between OS (with allocated type I error rate 0.03) and remaining key secondary endpoints (time to PSA progression and time to first use of new antineoplastic therapy with allocated type I error rate 0.02) was performed. Testing was performed only if the primary endpoint was statistically significant.

Comparison groups	Enzalutamide 160 mg v Placebo
Number of subjects included in analysis	1401
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.054
upper limit	0.081

Notes:

[4] - P-value was based on a stratified log-rank test by PSA doubling time (< 6 months, >= 6 months) and prior or concurrent use of a bone targeting agent (yes, no) as per IXRS. Threshold for significance at 0.02 level.

Secondary: Time to First Use of New Antineoplastic Therapy

End point title	Time to First Use of New Antineoplastic Therapy ^[5]
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End point description:

Time to first use of new antineoplastic therapy was defined as the time from randomization to first use of new antineoplastic for prostate cancer. Subjects not starting treatment with a new antineoplastic therapy at the time of analysis were right censored at the date of last assessment before the analysis data cutoff date for the purposes of analysis. Analysis was based on Kaplan-Meier estimates. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. The upper limit of 95% CI was not reached and has been denoted as 99999.

End point type	Secondary
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End point timeframe:

From randomization until first use of new antineoplastic therapy (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: months				
median (confidence interval 95%)	39.6 (37.7 to 99999)	17.7 (16.2 to 19.7)		

Statistical analyses

Statistical analysis title	Enzalutamide 160 mg Vs. Placebo
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Statistical analysis description:

To maintain the family-wise 2-sided type I error rate at 0.05, a parallel testing strategy between OS (with allocated type I error rate 0.03) and remaining key secondary endpoints (time to PSA progression and time to first use of new antineoplastic therapy with allocated type I error rate 0.02) was performed. Testing was performed only if the previous endpoint was statistically significant.

Comparison groups	Enzalutamide 160 mg v Placebo
Number of subjects included in analysis	1401
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.168
upper limit	0.258

Notes:

[6] - P-value was based on a stratified log-rank test by PSA doubling time (< 6 months, >= 6 months) and prior or concurrent use of a bone targeting agent (yes, no) as per IXRS. Threshold for significance at 0.02 level.

Secondary: Overall Survival

End point title	Overall Survival ^[7]
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End point description:

Overall survival (OS) was defined as the time (in months) from randomization to death from any cause. For subjects who were alive at the time of the analysis data cutoff, OS time was censored at the last date the subject was known to be alive or analysis data cutoff date, whichever was earlier. Subjects with no post baseline survival information were censored on the date of randomization. Analysis was based on Kaplan-Meier estimates. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. The upper limit of 95% CI was not reached and has been denoted as '99999'.

End point type	Secondary
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End point timeframe:

From randomization until death (up to a maximum of 68.8 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: months				
median (confidence interval 95%)	67.0 (64.0 to 99999)	56.3 (54.4 to 63.0)		

Statistical analyses

Statistical analysis title	Enzalutamide 160 mg Vs. Placebo
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Statistical analysis description:

To maintain family-wise 2-sided type I error rate at 0.05, parallel testing strategy between OS (with allocated type I error rate 0.03) and remaining key secondary endpoints (time to PSA progression and time to first use of new antineoplastic therapy with allocated type I error rate 0.02) was performed. OS tested at error rate 0.05 when both time to PSA progression and time to first use of new antineoplastic therapy were significant. When either failed to show significance, OS was tested at error 0.03.

Comparison groups	Enzalutamide 160 mg v Placebo
Number of subjects included in analysis	1401
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0011 ^[8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.734
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.608
upper limit	0.885

Notes:

[8] - P-value was based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone targeting agent (yes, no) as per interactive voice/web recognition system (IXRS).

Secondary: Time to Pain Progression

End point title	Time to Pain Progression ^[9]
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End point description:

Pain was assessed using the score from the Brief Pain Inventory-Short Form (BPI-SF) question 3: "Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours." Time to this event was defined as the time from randomization to onset of pain progression, where pain progression was defined as a 2-point or more increase from baseline in the question 3 score. Subjects without observed pain progression at the time of analysis were right censored at the date of last pain assessment for the purposes of analysis. Analysis was based on Kaplan-Meier estimates. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered.

End point type	Secondary
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End point timeframe:

From randomization until onset of pain progression (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: months				
median (confidence interval 95%)	18.5 (17.0 to 22.1)	18.4 (14.8 to 22.1)		

Statistical analyses

Statistical analysis title	Enzalutamide 160 mg Vs. Placebo
Comparison groups	Enzalutamide 160 mg v Placebo
Number of subjects included in analysis	1401
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6534 ^[10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.959
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.801
upper limit	1.149

Notes:

[10] - P-value was based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone targeting agent (yes, no) as per IXRS.

Secondary: Time to First Use of Cytotoxic Chemotherapy

End point title	Time to First Use of Cytotoxic Chemotherapy ^[11]
End point description:	Time to first use of cytotoxic chemotherapy was defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer. Subjects not starting treatment with a cytotoxic chemotherapy for prostate cancer at the time of analysis were right censored at the date of last assessment before the analysis data cutoff date for the purposes of analysis. Analysis was based on Kaplan-Meier estimates. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. The median and upper limit of 95% CI was not reached and has been denoted as 99999.
End point type	Secondary

End point timeframe:

From randomization up to the first use of cytotoxic chemotherapy (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: months				
median (confidence interval 95%)	99999 (38.1 to 99999)	39.7 (38.9 to 41.3)		

Statistical analyses

Statistical analysis title	Enzalutamide 160 mg Vs. Placebo
Comparison groups	Enzalutamide 160 mg v Placebo
Number of subjects included in analysis	1401
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.378
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.282
upper limit	0.507

Notes:

[12] - P-value was based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone targeting agent (yes, no) as per IXRS.

Secondary: Chemotherapy-Free Disease Specific Survival

End point title	Chemotherapy-Free Disease Specific Survival ^[13]
End point description:	Chemotherapy-free disease-specific survival was defined as the time from randomization to first use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer as assessed by the investigator. Subjects not starting treatment with a cytotoxic chemotherapy or not known to have died due to prostate cancer at the time of analysis were right censored at the date of last assessment before the analysis data cutoff date for the purposes of analysis. Analysis was based on Kaplan-Meier estimates. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. The upper limit of 95% CI was not reached and has been denoted as 99999.
End point type	Secondary

End point timeframe:

From randomization up to first use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: months				
median (confidence interval 95%)	39.6 (37.7 to 99999)	38.9 (30.9 to 41.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chemotherapy-Free Survival

End point title	Chemotherapy-Free Survival ^[14]
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End point description:

Chemotherapy-free survival was defined as the time from randomization to first use of cytotoxic chemotherapy for prostate cancer or death due to any cause. Subjects not starting treatment with a cytotoxic chemotherapy or not known to have died at the time of analysis were censored at the date of last assessment before the analysis data cutoff date for the purposes of analysis. Analysis was based on Kaplan-Meier estimates. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. The upper limit of 95% CI was not reached and has been denoted as 99999.

End point type	Secondary
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End point timeframe:

From randomization up to first use of cytotoxic chemotherapy for prostate cancer or death due to any cause (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: months				
median (confidence interval 95%)	38.1 (37.7 to 99999)	34.0 (30.3 to 39.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Prostate Specific Antigen (PSA) Response

End point title	Percentage of Subjects With Prostate Specific Antigen (PSA) Response ^[15]
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End point description:

PSA response was calculated at each visit as a decline from baseline in PSA (ng/mL) to the maximal PSA response with thresholds at 50% and 90%. Additionally, PSA response was assessed as a decline to undetectable levels, where undetectable level was defined as below the limit of quantification of the centrally assessed PSA results (the lower limit of quantification was 0.02 ng/mL). PSA response was

confirmed by a second consecutive value at least 3 weeks later. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered.

End point type	Secondary
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End point timeframe:

From randomization until first PSA progression (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: percentage of subjects				
number (confidence interval 95%)				
Decrease from Baseline \geq 50%	76.3 (73.5 to 79.0)	2.4 (1.2 to 4.2)		
Decrease from Baseline \geq 90%	55.9 (52.7 to 59.2)	0.4 (0.1 to 1.5)		
Decrease to Undetectable Level	9.6 (7.8 to 11.7)	0.0 (0 to 0.8)		

Statistical analyses

Statistical analysis title	Enzalutamide 160 mg Vs. Placebo
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Statistical analysis description:

Decrease from Baseline \geq 50%

Comparison groups	Enzalutamide 160 mg v Placebo
Number of subjects included in analysis	1401
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rate
Point estimate	73.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	70.91
upper limit	77.02

Notes:

[16] - P-value was based on a Cochran-Mantel-Haenszel mean score test stratified by PSA doubling time (<6 months, \geq 6 months) and prior concurrent use of a bone targeting agent (yes, no) as per IXRS.

Statistical analysis title	Enzalutamide 160 mg Vs. Placebo
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Statistical analysis description:

Decrease from Baseline \geq 90%

Comparison groups	Enzalutamide 160 mg v Placebo
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Number of subjects included in analysis	1401
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[17]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rate
Point estimate	55.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	52.28
upper limit	58.76

Notes:

[17] - P-value was based on a Cochran-Mantel-Haenszel mean score test stratified by PSA doubling time (<6 months, >= 6 months) and prior concurrent use of a bone targeting agent (yes, no) as per IXRS.

Statistical analysis title	Enzalutamide 160 mg Vs. Placebo
Statistical analysis description: Decrease to Undetectable Level	
Comparison groups	Enzalutamide 160 mg v Placebo
Number of subjects included in analysis	1401
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rate
Point estimate	9.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.75
upper limit	11.54

Notes:

[18] - P-value was based on a Cochran-Mantel-Haenszel mean score test stratified by PSA doubling time (<6 months, >= 6 months) and prior concurrent use of a bone targeting agent (yes, no) as per IXRS.

Secondary: Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Global Score

End point title	Change From Baseline in Quality of Life as Assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) Global Score ^[19]
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End point description:

The FACT-P questionnaire is a multidimensional, self-reported quality of life instrument consisting of 27 core items that assess subject function in 4 domains: physical, social/family, emotional, functional well-being, and supplemented by 12 site-specific items to assess prostate-related symptoms. Each item was rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as a global quality of life score which ranged from 0 to 156 where higher scores represented better quality of life. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points. Standard deviation was not analyzed since only 1 subject was evaluable and has been denoted by '99999'.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145, 161 and 177

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline(n=887,439)	119.5 (± 17.75)	120.8 (± 16.73)		
Change at Week 17(n=815,403)	-4.0 (± 14.03)	-3.0 (± 13.87)		
Change at Week 33(n=718,329)	-4.6 (± 14.82)	-3.5 (± 13.74)		
Change at Week 49(n=621,239)	-3.9 (± 14.70)	-5.0 (± 15.71)		
Change at Week 65(n=522,183)	-4.0 (± 15.84)	-5.7 (± 15.04)		
Change at Week 81(n=427,139)	-4.1 (± 15.01)	-7.5 (± 16.42)		
Change at Week 97(n=354,90)	-4.9 (± 15.31)	-5.9 (± 15.80)		
Change at Week 113(n=264,68)	-5.5 (± 16.07)	-5.8 (± 13.16)		
Change at Week 129(n=186,37)	-6.3 (± 17.33)	-8.1 (± 13.99)		
Change at Week 145(n=109,17)	-5.5 (± 18.75)	-9.8 (± 15.47)		
Change at Week 161(n=38,6)	-8.9 (± 19.88)	-7.0 (± 10.95)		
Change at Week 177(n=5,1)	-4.8 (± 13.19)	-5.0 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Mobility Domain Score

End point title	Number of Subjects With European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Mobility Domain Score ^[20]
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End point description:

EQ-5D-5L is a standardized instrument that measures health-related quality of life for men with prostate cancer. EQ-5D consists of EQ-5D descriptive system and EQ visual analogue scale (VAS). EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems. Number of subjects with various responses to the mobility questionnaire are reported. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline-No problem in walking(n=884,439)	578	298		
Baseline-slight problem in walking(n=884,439)	183	100		
Baseline-moderate problem in walking(n=884,439)	100	33		
Baseline-severe problem in walking(n=884,439)	21	7		
Baseline-unable to walk(n=884,439)	2	1		
Week 17-no problem in walking(n=840,419)	526	274		
Week 17-slight problem in walking(n=840,419)	190	88		
Week 17-moderate problem in walking(n=840,419)	87	50		
Week 17-severe problem in walking(n=840,419)	32	6		
Week 17-unable to walk(n=840,419)	5	1		
Week 33-no problem in walking(n=738,342)	431	223		
Week 33-slight problem in walking(n=738,342)	162	85		
Week 33-moderate problem in walking(n=738,342)	103	24		
Week 33-severe problem in walking(n=738,342)	36	10		
Week 33-unable to walk(n=738,342)	6	0		
Week 49-no problem in walking(n=635,250)	362	156		
Week 49-slight problem in walking(n=635,250)	158	57		
Week 49-moderate problem in walking(n=635,250)	86	27		
Week 49-severe problem in walking(n=635,250)	25	8		
Week 49-unable to walk(n=635,250)	4	2		
Week 65-no problem in walking(n=536,193)	319	121		
Week 65-slight problem in walking(n=536,193)	109	44		
Week 65-moderate problem in walking(n=536,193)	75	22		
Week 65-severe problem in walking(n=536,193)	29	6		
Week 65-unable to walk(n=536,193)	4	0		
Week 81-no problem in walking(n=435,148)	236	88		
Week 81-slight problem in walking(n=435,148)	111	39		
Week 81-moderate problem in walking(n=435,148)	61	15		
Week 81-severe problem in walking(n=435,148)	26	4		
Week 81-unable to walk(n=435,148)	1	2		

Week 97-no problem in walking(n=365,95)	189	59		
Week 97-slight problem in walking(n=365,95)	94	24		
Week 97-moderate problem in walking(n=365,95)	54	8		
Week 97-severe problem in walking(n=365,95)	22	4		
Week 97-unable to walk(n=365,95)	6	0		
Week 113-no problem in walking(n=275,73)	140	45		
Week 113-slight problem in walking(n=275,73)	76	14		
Week 113-moderate problem in walking(n=275,73)	41	11		
Week 113-severe problem in walking(n=275,73)	14	2		
Week 113-unable to walk(n=275,73)	4	1		
Week 129-no problem in walking(n=193,41)	94	26		
Week 129-slight problem in walking(n=193,41)	48	9		
Week 129-moderate problem in walking(n=193,41)	36	5		
Week 129-severe problem in walking(n=193,41)	15	1		
Week 129-unable to walk(n=193,41)	0	0		
Week 145-no problem in walking(n=116,21)	56	13		
Week 145-slight problem in walking(n=116,21)	35	5		
Week 145-moderate problem in walking(n=116,21)	18	2		
Week 145-severe problem in walking(n=116,21)	7	1		
Week 145-unable to walk(n=116,21)	0	0		
Week 161-no problem in walking(n=40,8)	22	2		
Week 161-slight problem in walking(n=40,8)	7	5		
Week 161-moderate problem in walking(n=40,8)	6	1		
Week 161-severe problem in walking(n=40,8)	5	0		
Week 161-unable to walk(n=40,8)	0	0		
Week 177-no problem in walking(n=6,1)	3	0		
Week 177-slight problem in walking(n=6,1)	2	1		
Week 177-moderate problem in walking(n=6,1)	1	0		
Week 177-severe problem in walking(n=6,1)	0	0		
Week 177-unable to walk(n=6,1)	0	0		

Statistical analyses

Secondary: Number of Subjects With European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Self-Care Domain Score

End point title	Number of Subjects With European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Self-Care Domain Score ^[21]
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End point description:

EQ-5D-5L is a standardized instrument that measures health-related quality of life for men with prostate cancer. EQ-5D consists of EQ-5D descriptive system and EQ VAS. EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems. Number of subjects with various responses to the self-care questionnaire are reported. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline (B), Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145, 161 and 177

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
B:no problems washing/dressing(n=884,439)	805	415		
B:slight problems washing/dressing(n=884,439)	51	23		
B:moderate problems washing/dressing(n=884,439)	22	1		
B:severe problems washing/dressing(n=884,439)	2	0		
B:unable to wash/dress(n=884,439)	4	0		
Week 17:no problems washing/dressing(n=840,419)	752	388		
Week 17:slightproblems washing/dressing(n=840,419)	60	26		
Week17:moderateproblems wash/dressing(n=840,419)	21	5		
Week 17:severe problems wash/dressing(n=840,419)	6	0		
Week 17:unable to wash/dress(n=840,419)	1	0		
Week 33:no problems washing/dressing(n=738,342)	642	310		
Week 33:slight problems wash/dressing(n=738,342)	64	20		
Week 33:moderate problems wash/dressing(n=738,342)	21	10		
Week 33:severe problems wash/dressing(n=738,342)	4	1		
Week 33:unable to wash/dress(n=738,342)	7	1		

Week 49:no problems wash/dressing(n=635,250)	546	230		
Week 49:slight problems wash/dressing(n=635,250)	59	9		
Week 49:moderate problems wash/dressing(n=635,250)	23	7		
Week 49:severe problems wash/dressing(n=635,250)	3	3		
Week 49:unable to wash/dress(n=635,250)	4	1		
Week 65:no problems wash/dressing(n=536,193)	453	179		
Week 65:slight problems wash/dressing(n=536,193)	57	11		
Week 65:moderate problems wash/dressing(n=536,193)	14	3		
Week 65:severe problems wash/dressing(n=536,193)	9	0		
Week 65:unable to wash/dress(n=536,193)	3	0		
Week 81:no problems wash/dressing(n=435,148)	356	132		
Week 81:slight problems wash/dressing(n=435,148)	57	11		
Week 81:moderate problems wash/dressing(n=435,148)	17	3		
Week 81:severe problems wash/dressing(n=435,148)	3	1		
Week 81:unable to wash/dress(n=435,148)	2	1		
Week 97:no problems wash/dressing(n=365,95)	292	85		
Week 97:slight problems wash/dressing(n=365,95)	51	8		
Week 97:moderate problems wash/dressing(n=365,95)	16	2		
Week 97:severe problems wash/dressing(n=365,95)	1	0		
Week 97:unable to wash/dress(n=365,95)	5	0		
Week 113:no problems wash/dressing(n=275,73)	214	60		
Week 113:slight problems wash/dressing(n=275,73)	46	7		
Week 113:moderate problems wash/dressing(n=275,73)	11	5		
Week 113:severe problems wash/dressing(n=275,73)	0	0		
Week 113:unable to wash/dress(n=275,73)	4	1		
Week 129:no problems wash/dressing(n=193,41)	147	35		
Week 129:slight problems wash/dressing(n=193,41)	28	5		
Week 129:moderate problems wash/dressing(n=193,41)	16	1		
Week 129:severe problems wash/dressing(n=193,41)	2	0		
Week 129:unable to wash/dress(n=193,41)	0	0		
Week 145:no problems wash/dressing(n=116,21)	92	15		

Week 145:slight problems wash/dressing(n=116,21)	16	5		
Week 145:moderate problems wash/dressing(n=116,21)	6	0		
Week 145:severe problems wash/dressing(n=116,21)	2	0		
Week 145:unable to wash/dress(n=116,21)	0	1		
Week 161:no problems wash/dressing(n=40,8)	33	7		
Week 161:slight problems wash/dressing(n=40,8)	3	0		
Week 161:moderate problems wash/dressing(n=40,8)	2	1		
Week 161:severe problems wash/dressing(n=40,8)	1	0		
Week 161:unable to wash/dress(n=40,8)	1	0		
Week 177:no problems wash/dressing(n=6,1)	3	1		
Week 177:slight problems wash/dressing(n=6,1)	3	0		
Week 177:moderate problems wash/dressing(n=6,1)	0	0		
Week 177:severe problems wash/dressing(n=6,1)	0	0		
Week 171:unable to wash/dress(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Usual Activities Domain Score

End point title	Number of Subjects With European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Usual Activities Domain Score ^[22]
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End point description:

EQ-5D-5L is a standardized instrument that measures health-related quality of life for men with prostate cancer. EQ-5D consists of EQ-5D descriptive system and EQ visual analogue scale (VAS). EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems. Number of subjects with various responses to the usual activities questionnaire are reported. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline (B), Weeks (W) 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
B:no problems doing usual activities(n=884,439)	646	356		
B:slightproblems doing usual activities(n=884,439)	167	64		
B:moderate problems(n=884,439)	56	14		
B:severe problems(n=884,439)	10	5		
B:unable to do usual activities(n=884,439)	5	0		
W 17:no problems in usual activities(n=840,419)	571	305		
W 17:slightproblems in usual activities(n=840,419)	181	89		
W 17:moderate problems(n=840,419)	60	24		
W 17:severe problems(n=840,419)	21	0		
W 17:unable to do usual activities(n=840,419)	7	1		
W 33:no problems doing usual activities(n=738,342)	474	249		
W 33:slightproblems in usual activities(n=738,342)	170	68		
W 33:moderate problems(n=738,342)	68	18		
W 33:severe problems(n=738,342)	21	7		
W 33:unable to do usual activities(n=738,342)	5	0		
W 49:no problems doing usual activities(n=635,250)	418	185		
W 49:slightproblems in usual activities(n=635,250)	137	43		
W 49:moderate problems(n=635,250)	55	14		
W 49:severe problems(n=635,250)	20	6		
W 49:unable to do usual activities(n=635,250)	5	2		
W 65:no problems doing usual activities(n=536,193)	338	136		
W 65:slightproblems in usual activities(n=536,193)	123	42		
W 65:moderate problems(n=536,193)	60	11		
W 65:severe problems(n=536,193)	5	4		
W 65:unable to do usual activities(n=536,193)	10	0		
W 81:no problems doing usual activities(n=435,148)	267	106		
W 81:slightproblems in usual activities(n=435,148)	105	29		
W 81:moderate problems(n=435,148)	49	7		
W 81:severe problems(n=435,148)	10	3		
W 81:unable to do usual activities(n=435,148)	4	3		
W 97:no problems doing usual activities(n=365,95)	224	69		
W 97:slightproblems in usual activities(n=365,95)	90	16		
W 97:moderate problems(n=365,95)	39	8		
W 97:severe problems(n=365,95)	9	0		

W 97:unable to do usual activities(n=365,95)	3	2		
W 113:no problems doing usual activities(n=275,73)	165	47		
W 113:slightproblems in usual activities(n=275,73)	69	16		
W 113:moderate problems(n=275,73)	33	6		
W 113:severe problems(n=275,73)	5	3		
W 113:unable to do usual activities(n=275,73)	3	1		
W 129:no problems doing usual activities(n=193,41)	108	30		
W 129:slightproblems in usual activities(n=193,41)	56	8		
W 129:moderate problems(n=193,41)	26	3		
W 129:severe problems(n=193,41)	3	0		
W 129:unable to do usual activities(n=193,41)	0	0		
W 145:no problems doing usual activities(n=116,21)	67	14		
W 145:slightproblems in usual activities(n=116,21)	35	4		
W 145:moderate problems(n=116,21)	11	2		
W 145:severe problems(n=116,21)	3	1		
W 145:unable to do usual activities(n=116,21)	0	0		
W 161:no problems doing usual activities(n=40,8)	23	5		
W 161:slightproblems in usual activities(n=40,8)	9	2		
W 161:moderate problems(n=40,8)	5	1		
W 161:severe problems(n=40,8)	2	0		
W 161:unable to do usual activities(n=40,8)	1	0		
W 177:no problems doing usual activities(n=6,1)	3	0		
W 177:slightproblems in usual activities(n=6,1)	2	1		
W 177:moderate problems(n=6,1)	1	0		
W 177:severe problems(n=6,1)	0	0		
W 177:unable to do usual activities(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Pain/Discomfort Domain Score

End point title	Number of Subjects With European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Pain/Discomfort Domain Score ^[23]
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End point description:

EQ-5D-5L is a standardized instrument that measures health-related quality of life for men with prostate cancer. EQ-5D consists of EQ-5D descriptive system and EQ visual analogue scale (VAS). EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and

anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems. Number of subjects with various responses to the pain/discomfort questionnaire are reported. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline (B), Weeks (W) 17, 33, 49, 65, 81, 97, 113, 129, 145, 161 and 177

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
B:no pain or discomfort(n=884,439)	546	292		
B:slight pain or discomfort(n=884,439)	240	117		
B:moderate pain or discomfort(n=884,439)	86	25		
B:severe pain or discomfort(n=884,439)	10	4		
B:extreme pain or discomfort(n=884,439)	2	1		
W17:no pain or discomfort(n=840,419)	464	248		
W17:slight pain or discomfort(n=840,419)	269	128		
W17: moderate pain or discomfort(n=840,419)	92	41		
W17:severe pain or discomfort(n=840,419)	13	2		
W17:extreme pain or discomfort(n=840,419)	2	0		
W33:no pain or discomfort(n=738,342)	405	204		
W33:slight pain or discomfort(n=738,342)	237	110		
W33:moderate pain or discomfort(n=738,342)	79	21		
W33:severe pain or discomfort(n=738,342)	16	7		
W33:extreme pain or discomfort(n=738,342)	1	0		
W49:no pain or discomfort(n=635,250)	340	134		
W49:slight pain or discomfort(n=635,250)	209	82		
W49:moderate pain or discomfort(n=635,250)	75	32		
W49:severe pain or discomfort(n=635,250)	10	1		
Week49:extreme pain or discomfort(n=635,250)	1	1		
W65:no pain or discomfort(n=536,193)	298	102		
W65:slight pain or discomfort(n=536,193)	162	72		
W65:moderate pain or discomfort(n=536,193)	61	15		

W65:severe pain or discomfort(n=536,193)	11	3		
W65:extreme pain or discomfort(n=536,193)	4	1		
W81:no pain or discomfort(n=435,148)	231	86		
W81:slight pain or discomfort(n=435,148)	133	45		
W81:moderate pain or discomfort(n=435,148)	61	13		
W81 :severe pain or discomfort(n=435,148)	10	2		
W81:extreme pain or discomfort(n=435,148)	0	2		
W97:no pain or discomfort(n=365,95)	202	58		
W97:slight pain or discomfort(n=365,95)	115	28		
W97:moderate pain or discomfort(n=365,95)	43	7		
W97:severe pain or discomfort(n=365,95)	5	2		
W97:extreme pain or discomfort(n=365,95)	0	0		
W113:no pain or discomfort(n=275,73)	152	47		
W113:slight pain or discomfort(n=275,73)	80	19		
W113:moderate pain or discomfort(n=275,73)	37	5		
W113:severe pain or discomfort(n=275,73)	6	2		
W113:extreme pain or discomfort(n=275,73)	0	0		
W129:no pain or discomfort(n=193,41)	108	27		
W129:slight pain or discomfort(n=193,41)	55	11		
W129:moderate pain or discomfort(n=193,41)	28	3		
W129:severe pain or discomfort(n=193,41)	2	0		
W129:extreme pain or discomfort(n=193,41)	0	0		
W145:no pain or discomfort(n=116,21)	62	12		
W145:slight pain or discomfort(n=116,21)	38	8		
W145:moderate pain or discomfort(n=116,21)	15	1		
W145:severe pain or discomfort(n=116,21)	1	0		
W145:extreme pain or discomfort(n=116,21)	0	0		
W161:no pain or discomfort(n=40,8)	24	2		
W161:slight pain or discomfort(n=40,8)	8	5		
W161:moderate pain or discomfort(n=40,8)	5	1		
W161:severe pain or discomfort(n=40,8)	3	0		
W161:extreme pain or discomfort(n=40,8)	0	0		
W177:no pain or discomfort(n=6,1)	3	0		
W177:slight pain or discomfort(n=6,1)	1	1		

W177:moderate pain or discomfort(n=6,1)	2	0		
W177:severe pain or discomfort(n=6,1)	0	0		
W177:extreme pain or discomfort(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Anxiety/ Depression Domain Score

End point title	Number of Subjects With European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Anxiety/ Depression Domain Score ^[24]
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End point description:

EQ-5D-5L is a standardized instrument that measures health-related quality of life for men with prostate cancer. EQ-5D consists of EQ-5D descriptive system and EQ visual analogue scale (VAS). EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems. Number of subjects with various responses to the anxiety/depression questionnaire are reported. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
B:not anxious or depressed(n=884,439)	595	310		
B:slightly anxious or depressed(n=884,439)	231	100		
B:moderately anxious or depressed(n=884,439)	51	24		
B:severely anxious or depressed(n=884,439)	6	5		
B:extremely anxious or depressed(n=884,439)	1	0		
W17:not anxious or depressed(n=840,419)	517	265		
W17:slightly anxious or depressed(n=840,419)	251	119		
W17:moderately anxious or depressed(n=840,419)	62	31		
W17:severely anxious or depressed(n=840,419)	7	4		

W17:extremely anxious or depressed(n=840,419)	3	0		
W33:not anxious or depressed(n=738,342)	458	223		
W33:slightly anxious or depressed(n=738,342)	208	89		
W33:moderately anxious or depressed(n=738,342)	61	23		
W33:severely anxious or depressed(n=738,342)	9	5		
W33:extremely anxious or depressed(n=738,342)	2	2		
W49:not anxious or depressed(n=635,250)	410	155		
W49:slightly anxious or depressed(n=635,250)	172	72		
W49:moderately anxious or depressed(n=635,250)	41	20		
W49:severely anxious or depressed(n=635,250)	8	2		
W49:extremely anxious or depressed(n=635,250)	4	1		
W65:not anxious or depressed(n=536,193)	336	128		
W65:slightly anxious or depressed(n=536,193)	149	56		
W65:moderately anxious or depressed(n=536,193)	43	8		
W65:severely anxious or depressed(n=536,193)	8	1		
W65:extremely anxious or depressed(n=536,193)	0	0		
W81:not anxious or depressed(n=435,148)	288	86		
W81:slightly anxious or depressed(n=435,148)	106	48		
W81:moderately anxious or depressed(n=435,148)	34	9		
W81:severely anxious or depressed(n=435,148)	7	3		
W81:extremely anxious or depressed(n=435,148)	0	2		
W97:not anxious or depressed(n=365,95)	220	61		
W97:slightly anxious or depressed(n=365,95)	114	27		
W97:moderately anxious or depressed(n=365,95)	26	6		
W97:severely anxious or depressed(n=365,95)	4	0		
W97:extremely anxious or depressed(n=365,95)	1	1		
W113:not anxious or depressed(n=275,73)	167	43		
W113:slightly anxious or depressed(n=275,73)	87	27		
W113:moderately anxious or depressed(n=275,73)	18	3		
W113:severely anxious or depressed(n=275,73)	3	0		
W113:extremely anxious or depressed(n=275,73)	0	0		

W129:not anxious or depressed(n=193,41)	121	28		
W129:slightly anxious or depressed(n=193,41)	51	10		
W129:moderately anxious or depressed(n=193,41)	18	2		
W129:severely anxious or depressed(n=193,41)	2	1		
W129:extremely anxious or depressed(n=193,41)	1	0		
W145:not anxious or depressed(n=116,21)	73	12		
W145:slightly anxious or depressed(n=116,21)	30	8		
W145:moderately anxious or depressed(n=116,21)	10	1		
W145:severely anxious or depressed(n=116,21)	2	0		
W145:extremely anxious or depressed(n=116,21)	1	0		
W161:not anxious or depressed(n=40,8)	23	3		
W161:slightly anxious or depressed(n=40,8)	16	4		
W161:moderately anxious or depressed(n=40,8)	0	1		
W161:severely anxious or depressed(n=40,8)	0	0		
W161:extremely anxious or depressed(n=40,8)	1	0		
W177:not anxious or depressed(n=6,1)	2	1		
W177:slightly anxious or depressed(n=6,1)	2	0		
W177:moderately anxious or depressed(n=6,1)	2	0		
W177:severely anxious or depressed(n=6,1)	0	0		
W177:extremely anxious or depressed(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Overall Health Status Visual Analog Score (VAS)

End point title	European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Overall Health Status Visual Analog Score (VAS) ^[25]
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End point description:

EQ-5D-5L is a standardized instrument that measures health-related quality of life for men with prostate cancer. EQ-5D consists of EQ-5D descriptive system and EQ VAS. EQ-5D-5L-VAS records subject's self-rated health on a vertical VAS that allows them to indicate their health state that can range from 0 (worst imaginable) to 100 (best imaginable), higher scores indicating a better health state. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points. Standard deviation was not analysed since only 1 subject was evaluable and has been denoted by '99999'.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=884,439)	76.2 (± 16.92)	77.5 (± 15.97)		
Week 17 (n=840,419)	74.7 (± 17.19)	74.9 (± 16.79)		
Week 33 (n=738,342)	74.6 (± 16.69)	74.0 (± 17.51)		
Week 49 (n=635,250)	74.7 (± 18.02)	73.7 (± 18.28)		
Week 65 (n=536,193)	74.5 (± 17.79)	73.0 (± 17.11)		
Week 81 (n=435,148)	75.5 (± 17.06)	73.3 (± 16.82)		
Week 97 (n=365,95)	74.4 (± 17.39)	75.2 (± 17.88)		
Week 113 (n=275,73)	73.6 (± 18.05)	74.7 (± 15.06)		
Week 129 (n=193,41)	72.8 (± 18.25)	77.1 (± 12.83)		
Week 145 (n=116,21)	75.3 (± 17.02)	74.2 (± 18.13)		
Week 161 (n=40,8)	74.6 (± 21.28)	73.8 (± 17.60)		
Week 177 (n=6,1)	74.5 (± 19.31)	69.0 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 31

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 31 ^[26]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 31 are reported. Question 31 was following: "Have you had to urinate frequently during the day?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	285	162		
Baseline: a little(n=884,439)	348	160		
Baseline: quite a bit(n=884,439)	207	92		
Baseline: very much(n=884,439)	44	25		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	275	134		
Week 17: a little(n=839,419)	324	168		
Week 17: quite a bit(n=839,419)	194	90		
Week 17: very much(n=839,419)	46	27		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	236	105		
Week 33: a little(n=737,341)	285	145		
Week 33: quite a bit(n=737,341)	176	70		
Week 33: very much(n=737,341)	40	21		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	200	82		
Week 49: a little(n=635,250)	260	92		
Week 49: quite a bit(n=635,250)	148	67		
Week 49: very much(n=635,250)	27	9		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	172	54		
Week 65: a little(n=536,193)	209	79		
Week 65: quite a bit(n=536,193)	125	48		
Week 65: very much(n=536,193)	30	12		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	141	46		
Week 81: a little(n=434,148)	181	60		
Week 81: quite a bit(n=434,148)	92	31		
Week 81: very much(n=434,148)	20	11		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	118	33		
Week 97: a little(n=365,95)	146	40		
Week 97: quite a bit(n=365,95)	80	19		
Week 97: very much(n=365,95)	21	3		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	101	17		
Week 113: a little(n=275,73)	112	40		
Week 113: quite a bit(n=275,73)	46	14		
Week 113: very much(n=275,73)	16	2		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	70	11		
Week 129: a little(n=192,41)	79	16		

Week 129: quite a bit(n=192,41)	39	10		
Week 129: very much(n=192,41)	4	4		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	42	2		
Week 145: a little(n=116,21)	51	14		
Week 145: quite a bit(n=116,21)	20	4		
Week 145: very much(n=116,21)	3	1		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	9	2		
Week 161: a little(n=40,8)	20	4		
Week 161: quite a bit(n=40,8)	7	1		
Week 161: very much(n=40,8)	4	1		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	0	0		
Week 177: a little(n=6,1)	4	1		
Week 177: quite a bit(n=6,1)	2	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 32

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 32 ^[27]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 32 are reported. Question 32 was following: "Have you had to urinate frequently at night?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	193	108		
Baseline: a little(n=884,439)	423	195		
Baseline: quite a bit(n=884,439)	200	103		
Baseline: very much(n=884,439)	68	33		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all (n=839,419)	194	88		
Week 17: a little (n=839,419)	407	199		
Week 17: quite a bit (n=839,419)	184	98		
Week 17: very much (n=839,419)	54	34		
Week 17: not answered (n=839,419)	0	0		
Week 33: not at all(n=737,341)	173	83		
Week 33: a little(n=737,341)	351	161		
Week 33: quite a bit(n=737,341)	169	69		
Week 33: very much(n=737,341)	44	28		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	148	59		
Week 49: a little(n=635,250)	313	116		
Week 49: quite a bit(n=635,250)	141	59		
Week 49: very much(n=635,250)	33	16		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	118	41		
Week 65: a little(n=536,193)	266	89		
Week 65: quite a bit(n=536,193)	111	48		
Week 65: very much(n=536,193)	41	15		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	91	38		
Week 81: a little(n=434,148)	231	60		
Week 81: quite a bit(n=434,148)	89	38		
Week 81: very much(n=434,148)	23	12		
Week 81: not answeredv(n=434,148)	0	0		
Week 97: not at all(n=365,95)	88	19		
Week 97: a little(n=365,95)	169	53		
Week 97: quite a bit(n=365,95)	82	19		
Week 97: very much(n=365,95)	26	4		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	67	16		
Week 113: a little(n=275,73)	137	32		
Week 113: quite a bit(n=275,73)	54	23		
Week 113: very much(n=275,73)	17	2		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	50	9		
Week 129: a little(n=192,41)	97	18		
Week 129: quite a bit(n=192,41)	37	10		
Week 129: very much(n=192,41)	8	4		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	31	2		
Week 145: a little(n=116,21)	59	14		

Week 145: quite a bit(n=116,21)	24	5		
Week 145: very much(n=116,21)	2	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	9	0		
Week 161: a little(n=40,8)	23	7		
Week 161: quite a bit(n=40,8)	5	0		
Week 161: very much(n=40,8)	3	1		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	2	0		
Week 177: a little(n=6,1)	2	1		
Week 177: quite a bit(n=6,1)	2	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 33

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 33 ^[28]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 33 are reported. Question 33 was following: "When you felt the urge to pass urine, did you have to hurry to get to the toilet?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	406	197		
Baseline: a little(n=884,439)	266	147		
Baseline: quite a bit(n=884,439)	150	70		
Baseline: very much(n=884,439)	62	25		

Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	350	191		
Week 17: a little(n=839,419)	297	150		
Week 17: quite a bit(n=839,419)	127	55		
Week 17: very much(n=839,419)	65	23		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	279	147		
Week 33: a little(n=737,341)	278	126		
Week 33: quite a bit(n=737,341)	126	48		
Week 33: very much(n=737,341)	54	20		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	272	100		
Week 49: a little(n=635,250)	222	95		
Week 49: quite a bit(n=635,250)	96	38		
Week 49: very much(n=635,250)	45	17		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	213	76		
Week 65: a little(n=536,193)	213	72		
Week 65: quite a bit(n=536,193)	71	31		
Week 65: very much(n=536,193)	39	14		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	181	63		
Week 81: a little(n=434,148)	157	52		
Week 81: quite a bit(n=434,148)	69	27		
Week 81: very much(n=434,148)	27	6		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	146	40		
Week 97: a little(n=365,95)	131	40		
Week 97: quite a bit(n=365,95)	59	12		
Week 97: very much(n=365,95)	29	3		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	114	29		
Week 113: a little(n=275,73)	106	34		
Week 113: quite a bit(n=275,73)	40	9		
Week 113: very much(n=275,73)	15	1		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	86	10		
Week 129: a little (n=192,41)	72	21		
Week 129: quite a bit(n=192,41)	26	6		
Week 129: very much(n=192,41)	8	4		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	51	5		
Week 145: a little(n=116,21)	39	12		
Week 145: quite a bit(n=116,21)	21	4		
Week 145: very much(n=116,21)	5	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	17	0		
Week 161: a little(n=40,8)	19	5		
Week 161: quite a bit(n=40,8)	3	3		
Week 161: very much(n=40,8)	1	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	2	0		

Week 177: a little(n=6,1)	1	1		
Week 177: quite a bit(n=6,1)	3	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 34

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 34 ^[29]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 34 are reported. Question 34 was following: "Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	479	235		
Baseline: a little(n=884,439)	273	146		
Baseline: quite a bit(n=884,439)	93	40		
Baseline: very much(n=884,439)	39	18		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	437	214		
Week 17: a little(n=839,419)	295	144		
Week 17: quite a bit(n=839,419)	75	45		
Week 17: very much(n=839,419)	32	16		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	392	180		
Week 33: a little(n=737,341)	246	112		
Week 33: quite a bit(n=737,341)	75	33		

Week 33: very much(n=737,341)	24	16		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	340	119		
Week 49: a little(n=635,250)	211	94		
Week 49: quite a bit(n=635,250)	65	28		
Week 49: very much(n=635,250)	19	9		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	286	92		
Week 65: a little(n=536,193)	183	67		
Week 65: quite a bit(n=536,193)	47	29		
Week 65: very much(n=536,193)	20	5		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	221	70		
Week 81: a little(n=434,148)	165	55		
Week 81: quite a bit(n=434,148)	37	18		
Week 81: very much(n=434,148)	11	5		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	185	47		
Week 97: a little(n=365,95)	122	33		
Week 97: quite a bit(n=365,95)	43	14		
Week 97: very much(n=365,95)	15	1		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	135	31		
Week 113: a little(n=275,73)	102	33		
Week 113: quite a bit(n=275,73)	29	7		
Week 113: very much(n=275,73)	9	2		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	103	13		
Week 129: a little(n=192,41)	67	23		
Week 129: quite a bit(n=192,41)	19	4		
Week 129: very much(n=192,41)	3	1		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	59	9		
Week 145: a little(n=116,21)	44	10		
Week 145: quite a bit(n=116,21)	11	1		
Week 145: very much(n=116,21)	2	1		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	21	2		
Week 161: a little(n=40,8)	16	5		
Week 161: quite a bit(n=40,8)	3	0		
Week 161: very much(n=40,8)	0	1		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	3	0		
Week 177: a little(n=6,1)	1	1		
Week 177: quite a bit(n=6,1)	2	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 35

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 35 ^[30]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 35 are reported. Question 35 was following: "Have you had difficulty going out of the house because you needed to be close to a toilet?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145, 161 and 177

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	646	330		
Baseline: a little(n=884,439)	177	84		
Baseline: quite a bit(n=884,439)	45	18		
Baseline: very much(n=884,439)	16	7		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	604	295		
Week 17: a little(n=839,419)	174	100		
Week 17: quite a bit(n=839,419)	46	15		
Week 17: very much(n=839,419)	15	9		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	501	242		
Week 33: a little(n=737,341)	171	74		
Week 33: quite a bit(n=737,341)	50	20		
Week 33: very much(n=737,341)	15	5		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	436	174		
Week 49: a little(n=635,250)	153	53		
Week 49: quite a bit(n=635,250)	38	20		
Week 49: very much(n=635,250)	8	3		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	369	132		
Week 65: a little(n=536,193)	125	50		

Week 65: quite a bit(n=536,193)	28	9		
Week 65: very much(n=536,193)	14	2		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	308	105		
Week 81: a little(n=434,148)	94	35		
Week 81: quite a bit(n=434,148)	23	8		
Week 81: very much(n=434,148)	9	0		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	241	67		
Week 97: a little(n=365,95)	91	21		
Week 97: quite a bit(n=365,95)	26	6		
Week 97: very much(n=365,95)	7	1		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	180	47		
Week 113: a little(n=275,73)	70	21		
Week 113: quite a bit(n=275,73)	18	5		
Week 113: very much(n=275,73)	7	0		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	131	26		
Week 129: a little(n=192,41)	48	13		
Week 129: quite a bit(n=192,41)	8	1		
Week 129: very much(n=192,41)	5	1		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	74	13		
Week 145: a little(n=116,21)	36	6		
Week 145: quite a bit(n=116,21)	6	0		
Week 145: very much(n=116,21)	0	2		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	24	4		
Week 161: a little(n=40,8)	13	4		
Week 161: quite a bit(n=40,8)	3	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	3	0		
Week 177: a little(n=6,1)	3	1		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 36

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 36 ^[31]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 36 are reported. Question 36 was following: "Have you had any unintentional release (leakage) of urine?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	550	283		
Baseline: a little(n=884,439)	273	124		
Baseline: quite a bit(n=884,439)	36	20		
Baseline: very much(n=884,439)	25	12		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	511	255		
Week 17: a little(n=839,419)	264	126		
Week 17: quite a bit(n=839,419)	39	27		
Week 17: very much(n=839,419)	25	11		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	428	208		
Week 33: a little(n=737,341)	246	104		
Week 33: quite a bit(n=737,341)	34	19		
Week 33: very much(n=737,341)	29	10		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	369	146		
Week 49: a little(n=635,250)	209	78		
Week 49: quite a bit(n=635,250)	41	22		
Week 49: very much(n=635,250)	16	4		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	307	115		
Week 65: a little(n=536,193)	170	66		
Week 65: quite a bit(n=536,193)	47	8		
Week 65: very much(n=536,193)	12	4		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	248	93		
Week 81: a little(n=434,148)	158	41		
Week 81: quite a bit(n=434,148)	23	11		
Week 81: very much(n=434,148)	5	3		
Week 81: not answered(n=434,148)	0	0		

Week 97: not at all(n=365,95)	195	55		
Week 97: a little(n=365,95)	134	33		
Week 97: quite a bit(n=365,95)	25	7		
Week 97: very much(n=365,95)	11	0		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	160	42		
Week 113: a little(n=275,73)	91	28		
Week 113: quite a bit(n=275,73)	17	3		
Week 113: very much(n=275,73)	7	0		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	109	22		
Week 129: a little(n=192,41)	68	13		
Week 129: quite a bit(n=192,41)	13	5		
Week 129: very much(n=192,41)	2	1		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	58	9		
Week 145: a little(n=116,21)	45	11		
Week 145: quite a bit(n=116,21)	10	0		
Week 145: very much(n=116,21)	3	1		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	18	3		
Week 161: a little(n=40,8)	21	4		
Week 161: quite a bit(n=40,8)	0	1		
Week 161: very much(n=40,8)	1	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	1	0		
Week 177: a little(n=6,1)	3	1		
Week 177: quite a bit(n=6,1)	1	0		
Week 177: very much(n=6,1)	1	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 37

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 37 ^[32]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 37 are reported. Question 37 was following: "Did you have pain when you urinated?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	775	380		
Baseline: a little(n=884,439)	92	47		
Baseline: quite a bit(n=884,439)	10	8		
Baseline: very much(n=884,439)	7	4		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	762	351		
Week 17: a little(n=839,419)	65	58		
Week 17: quite a bit(n=839,419)	12	8		
Week 17: very much(n=839,419)	0	2		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	662	291		
Week 33: a little(n=737,341)	63	39		
Week 33: quite a bit(n=737,341)	11	8		
Week 33: very much(n=737,341)	1	3		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	577	209		
Week 49: a little(n=635,250)	49	34		
Week 49: quite a bit(n=635,250)	6	3		
Week 49: very much(n=635,250)	3	4		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	492	161		
Week 65: a little(n=536,193)	32	29		
Week 65: quite a bit(n=536,193)	9	2		
Week 65: very much(n=536,193)	3	1		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	389	119		
Week 81: a little(n=434,148)	40	27		
Week 81: quite a bit(n=434,148)	4	2		
Week 81: very much(n=434,148)	1	0		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	332	84		
Week 97: a little(n=365,95)	28	11		
Week 97: quite a bit(n=365,95)	4	0		
Week 97: very much(n=365,95)	1	0		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	247	57		
Week 113: a little(n=275,73)	26	13		
Week 113: quite a bit(n=275,73)	1	3		
Week 113: very much(n=275,73)	1	0		
Week 113: not answered(n=275,73)	0	0		

Week 129: not at all(n=192,41)	173	34		
Week 129: a little(n=192,41)	16	7		
Week 129: quite a bit(n=192,41)	1	0		
Week 129: very much(n=192,41)	2	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	102	15		
Week 145: a little(n=116,21)	14	6		
Week 145: quite a bit(n=116,21)	0	0		
Week 145: very much(n=116,21)	0	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	36	6		
Week 161: a little(n=40,8)	3	1		
Week 161: quite a bit(n=40,8)	1	1		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	6	0		
Week 177: a little(n=6,1)	0	1		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 38

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 38 ^[33]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 38 are reported. Question 38 was following: "Has wearing an incontinence aid been a problem for you?" This question was answered by only those subjects who wore incontinence aid. The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=144,67)	83	37		
Baseline: a little(n=144,67)	40	19		
Baseline: quite a bit(n=144,67)	15	3		
Baseline: very much(n=144,67)	6	8		
Baseline: not answered(n=144,67)	0	0		
Week 17: not at all(n=839,419)	77	34		
Week 17: a little(n=839,419)	48	21		
Week 17: quite a bit(n=839,419)	15	7		
Week 17: very much(n=839,419)	6	6		
Week 17: not answered(n=839,419)	693	351		
Week 33: not at all(n=737,341)	76	30		
Week 33: a little(n=737,341)	47	28		
Week 33: quite a bit(n=737,341)	16	4		
Week 33: very much(n=737,341)	5	4		
Week 33: not answered(n=737,341)	593	275		
Week 49: not at all(n=635,250)	73	18		
Week 49: a little(n=635,250)	43	16		
Week 49: quite a bit(n=635,250)	12	9		
Week 49: very much(n=635,250)	4	2		
Week 49: not answered(n=635,250)	503	205		
Week 65: not at all(n=536,193)	63	12		
Week 65: a little(n=536,193)	40	17		
Week 65: quite a bit(n=536,193)	9	5		
Week 65: very much(n=536,193)	3	1		
Week 65: not answered(n=536,193)	421	158		
Week 81: not at all(n=434,148)	52	15		
Week 81: a little(n=434,148)	33	9		
Week 81: quite a bit(n=434,148)	10	1		
Week 81: very much(n=434,148)	3	3		
Week 81: not answered(n=434,148)	336	120		
Week 97: not at all(n=365,95)	50	8		
Week 97: a little(n=365,95)	28	8		
Week 97: quite a bit(n=365,95)	7	2		
Week 97: very much(n=365,95)	3	0		
Week 97: not answered(n=365,95)	277	77		
Week 113: not at all(n=275,73)	31	12		
Week 113: a little(n=275,73)	18	7		
Week 113: quite a bit(n=275,73)	8	2		
Week 113: very much(n=275,73)	2	0		
Week 113: not answered(n=275,73)	216	52		
Week 129: not at all(n=192,41)	27	5		
Week 129: a little(n=192,41)	18	5		
Week 129: quite a bit(n=192,41)	2	1		
Week 129: very much(n=192,41)	0	0		
Week 129: not answered(n=192,41)	145	30		
Week 145: not at all(n=116,21)	16	2		
Week 145: a little(n=116,21)	10	4		

Week 145: quite a bit(n=116,21)	5	0		
Week 145: very much(n=116,21)	0	0		
Week 145: not answered(n=116,21)	85	15		
Week 161: not at all(n=40,8)	10	1		
Week 161: a little(n=40,8)	3	2		
Week 161: quite a bit(n=40,8)	1	1		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	26	4		
Week 177: not at all(n=6,1)	3	0		
Week 177: a little(n=6,1)	1	0		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 39

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 39 ^[34]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 39 are reported. Question 39 was following: "Have your daily activities been limited by your urinary problems?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	666	338		
Baseline: a little(n=884,439)	173	80		
Baseline: quite a bit(n=884,439)	35	11		
Baseline: very much(n=884,439)	10	10		

Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	632	305		
Week 17: a little(n=839,419)	160	99		
Week 17: quite a bit(n=839,419)	36	6		
Week 17: very much(n=839,419)	11	9		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	523	242		
Week 33: a little(n=737,341)	172	79		
Week 33: quite a bit(n=737,341)	31	14		
Week 33: very much(n=737,341)	11	6		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	444	173		
Week 49: a little(n=635,250)	152	58		
Week 49: quite a bit(n=635,250)	31	18		
Week 49: very much(n=635,250)	8	1		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	382	128		
Week 65: a little(n=536,193)	124	51		
Week 65: quite a bit(n=536,193)	20	12		
Week 65: very much(n=536,193)	10	2		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	310	103		
Week 81: a little(n=434,148)	98	35		
Week 81: quite a bit(n=434,148)	21	8		
Week 81: very much(n=434,148)	5	2		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	242	72		
Week 97: a little(n=365,95)	100	18		
Week 97: quite a bit(n=365,95)	18	4		
Week 97: very much(n=365,95)	5	1		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	188	54		
Week 113: a little(n=275,73)	71	14		
Week 113: quite a bit(n=275,73)	13	3		
Week 113: very much(n=275,73)	3	2		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	127	25		
Week 129: a little(n=192,41)	55	14		
Week 129: quite a bit(n=192,41)	7	1		
Week 129: very much(n=192,41)	3	1		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	77	11		
Week 145: a little(n=116,21)	34	9		
Week 145: quite a bit(n=116,21)	4	1		
Week 145: very much(n=116,21)	1	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	27	2		
Week 161: a little(n=40,8)	10	6		
Week 161: quite a bit(n=40,8)	3	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	3	0		

Week 177: a little(n=6,1)	3	1		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 40

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 40 ^[35]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 40 are reported. Question 40 was following: "Have your daily activities been limited by your bowel problems?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	758	393		
Baseline: a little(n=884,439)	112	40		
Baseline: quite a bit(n=884,439)	9	4		
Baseline: very much(n=884,439)	5	2		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	707	352		
Week 17: a little(n=839,419)	107	57		
Week 17: quite a bit(n=839,419)	19	6		
Week 17: very much(n=839,419)	6	4		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	621	292		
Week 33: a little(n=737,341)	98	40		
Week 33: quite a bit(n=737,341)	14	8		

Week 33: very much(n=737,341)	4	1		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	525	211		
Week 49: a little(n=635,250)	88	29		
Week 49: quite a bit(n=635,250)	20	7		
Week 49: very much(n=635,250)	2	3		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	441	165		
Week 65: a little(n=536,193)	78	24		
Week 65: quite a bit(n=536,193)	11	3		
Week 65: very much(n=536,193)	6	1		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	360	121		
Week 81: a little(n=434,148)	56	23		
Week 81: quite a bit(n=434,148)	17	3		
Week 81: very much(n=434,148)	1	1		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	289	84		
Week 97: a little(n=365,95)	58	11		
Week 97: quite a bit(n=365,95)	17	0		
Week 97: very much(n=365,95)	1	0		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	219	62		
Week 113: a little(n=275,73)	46	11		
Week 113: quite a bit(n=275,73)	8	0		
Week 113: very much(n=275,73)	2	0		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	153	36		
Week 129: a little(n=192,41)	33	5		
Week 129: quite a bit(n=192,41)	5	0		
Week 129: very much(n=192,41)	1	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	93	17		
Week 145: a little(n=116,21)	19	4		
Week 145: quite a bit(n=116,21)	4	0		
Week 145: very much(n=116,21)	0	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	29	8		
Week 161: a little(n=40,8)	9	0		
Week 161: quite a bit(n=40,8)	2	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	4	1		
Week 177: a little(n=6,1)	2	0		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 41

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 41 ^[36]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 41 are reported. Question 41 was following: "Have you had any unintentional release (leakage) of stools?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145, 161 and 177

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	794	404		
Baseline: a little(n=884,439)	78	32		
Baseline: quite a bit(n=884,439)	11	2		
Baseline: very much(n=884,439)	1	1		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	751	372		
Week 17: a little(n=839,419)	79	43		
Week 17: quite a bit(n=839,419)	8	3		
Week 17: very much(n=839,419)	1	1		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	638	307		
Week 33: a little(n=737,341)	92	32		
Week 33: quite a bit(n=737,341)	4	1		
Week 33: very much(n=737,341)	3	1		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	554	221		
Week 49: a little(n=635,250)	73	25		
Week 49: quite a bit(n=635,250)	5	4		
Week 49: very much(n=635,250)	3	0		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	467	175		
Week 65: a little(n=536,193)	57	16		

Week 65: quite a bit(n=536,193)	9	1		
Week 65: very much(n=536,193)	3	1		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	380	136		
Week 81: a little(n=434,148)	51	12		
Week 81: quite a bit(n=434,148)	2	0		
Week 81: very much(n=434,148)	1	0		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	315	86		
Week 97: a little(n=365,95)	47	9		
Week 97: quite a bit(n=365,95)	3	0		
Week 97: very much(n=365,95)	0	0		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	233	66		
Week 113: a little(n=275,73)	40	7		
Week 113: quite a bit(n=275,73)	2	0		
Week 113: very much(n=275,73)	0	0		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	167	39		
Week 129: a little(n=192,41)	25	2		
Week 129: quite a bit(n=192,41)	0	0		
Week 129: very much(n=192,41)	0	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	93	20		
Week 145: a little(n=116,21)	22	1		
Week 145: quite a bit(n=116,21)	0	0		
Week 145: very much(n=116,21)	1	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	30	8		
Week 161: a little(n=40,8)	9	0		
Week 161: quite a bit(n=40,8)	0	0		
Week 161: very much(n=40,8)	1	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	4	1		
Week 177: a little(n=6,1)	2	0		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 42

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 42 ^[37]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 42 are reported. Question 42 was following: "Have you had blood in your stools?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	836	422		
Baseline: a little(n=884,439)	48	17		
Baseline: quite a bit(n=884,439)	0	0		
Baseline: very much(n=884,439)	0	0		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	801	399		
Week 17: a little(n=839,419)	36	18		
Week 17: quite a bit(n=839,419)	2	2		
Week 17: very much(n=839,419)	0	0		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	707	330		
Week 33: a little(n=737,341)	29	11		
Week 33: quite a bit(n=737,341)	1	0		
Week 33: very much(n=737,341)	0	0		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	608	245		
Week 49: a little(n=635,250)	27	5		
Week 49: quite a bit(n=635,250)	0	0		
Week 49: very much(n=635,250)	0	0		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	514	180		
Week 65: a little(n=536,193)	19	13		
Week 65: quite a bit(n=536,193)	3	0		
Week 65: very much(n=536,193)	0	0		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	420	143		
Week 81: a little(n=434,148)	14	4		
Week 81: quite a bit(n=434,148)	0	1		
Week 81: very much(n=434,148)	0	0		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	357	93		

Week 97: a little(n=365,95)	8	2		
Week 97: quite a bit(n=365,95)	0	0		
Week 97: very much(n=365,95)	0	0		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	262	72		
Week 113: a little(n=275,73)	13	1		
Week 113: quite a bit(n=275,73)	0	0		
Week 113: very much(n=275,73)	0	0		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	186	41		
Week 129: a little(n=192,41)	5	0		
Week 129: quite a bit(n=192,41)	1	0		
Week 129: very much(n=192,41)	0	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	114	21		
Week 145: a little(n=116,21)	2	0		
Week 145: quite a bit(n=116,21)	0	0		
Week 145: very much(n=116,21)	0	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	38	8		
Week 161: a little(n=40,8)	2	0		
Week 161: quite a bit(n=40,8)	0	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	6	1		
Week 177: a little(n=6,1)	0	0		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 43

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 43 ^[38]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 43 are reported. Question 43 was following: "Did you have a bloated feeling in your abdomen?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	667	320		
Baseline: a little(n=884,439)	190	103		
Baseline: quite a bit(n=884,439)	22	16		
Baseline: very much(n=884,439)	5	0		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	601	283		
Week 17: a little(n=839,419)	199	121		
Week 17: quite a bit(n=839,419)	31	13		
Week 17: very much(n=839,419)	8	2		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	526	235		
Week 33: a little(n=737,341)	183	95		
Week 33: quite a bit(n=737,341)	22	8		
Week 33: very much(n=737,341)	6	3		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	449	174		
Week 49: a little(n=635,250)	163	63		
Week 49: quite a bit(n=635,250)	20	11		
Week 49: very much(n=635,250)	3	2		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	381	135		
Week 65: a little(n=536,193)	132	51		
Week 65: quite a bit(n=536,193)	19	7		
Week 65: very much(n=536,193)	4	0		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	304	103		
Week 81: a little(n=434,148)	110	44		
Week 81: quite a bit(n=434,148)	18	1		
Week 81: very much(n=434,148)	2	0		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	258	72		
Week 97: a little(n=365,95)	87	23		
Week 97: quite a bit(n=365,95)	19	0		
Week 97: very much(n=365,95)	1	0		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	199	55		
Week 113: a little(n=275,73)	66	18		
Week 113: quite a bit(n=275,73)	9	0		
Week 113: very much(n=275,73)	1	0		
Week 113: not answered(n=275,73)	0	0		

Week 129: not at all(n=192,41)	139	25		
Week 129: a little(n=192,41)	43	16		
Week 129: quite a bit(n=192,41)	8	0		
Week 129: very much(n=192,41)	2	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	87	13		
Week 145: a little(n=116,21)	24	8		
Week 145: quite a bit(n=116,21)	4	0		
Week 145: very much(n=116,21)	1	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	33	6		
Week 161: a little(n=40,8)	7	2		
Week 161: quite a bit(n=40,8)	0	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	4	0		
Week 177: a little(n=6,1)	2	1		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 44

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 44 ^[39]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 44 are reported. Question 44 was following: "Did you have hot flushes?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	374	177		
Baseline: a little(n=884,439)	314	166		
Baseline: quite a bit(n=884,439)	151	68		
Baseline: very much(n=884,439)	45	28		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	265	182		
Week 17: a little(n=839,419)	311	153		
Week 17: quite a bit(n=839,419)	189	62		
Week 17: very much(n=839,419)	74	22		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	253	144		
Week 33: a little(n=737,341)	268	116		
Week 33: quite a bit(n=737,341)	155	60		
Week 33: very much(n=737,341)	61	21		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	227	112		
Week 49: a little(n=635,250)	235	94		
Week 49: quite a bit(n=635,250)	130	30		
Week 49: very much(n=635,250)	43	14		
Week 49: not answered (n=635,250)	0	0		
Week 65: not at all(n=536,193)	203	79		
Week 65: a little(n=536,193)	194	77		
Week 65: quite a bit(n=536,193)	104	30		
Week 65: very much(n=536,193)	35	7		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	175	69		
Week 81: a little(n=434,148)	157	58		
Week 81: quite a bit(n=434,148)	75	16		
Week 81: very much(n=434,148)	27	5		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	155	48		
Week 97: a little(n=365,95)	126	34		
Week 97: quite a bit(n=365,95)	57	12		
Week 97: very much(n=365,95)	27	1		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	114	33		
Week 113: a little(n=275,73)	102	24		
Week 113: quite a bit(n=275,73)	44	14		
Week 113: very much(n=275,73)	15	2		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	84	22		
Week 129: a little(n=192,41)	74	16		
Week 129: quite a bit(n=192,41)	23	3		
Week 129: very much(n=192,41)	11	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	45	10		
Week 145: a little(n=116,21)	46	10		

Week 145: quite a bit(n=116,21)	18	0		
Week 145: very much(n=116,21)	7	1		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	18	3		
Week 161: a little(n=40,8)	14	3		
Week 161: quite a bit(n=40,8)	5	2		
Week 161: very much(n=40,8)	3	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	3	0		
Week 177: a little(n=6,1)	0	0		
Week 177: quite a bit(n=6,1)	1	1		
Week 177: very much(n=6,1)	2	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 45

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 45 ^[40]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 45 are reported. Question 45 was following: "Have you had sore or enlarged nipples or breasts?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	688	333		
Baseline: a little(n=884,439)	146	80		
Baseline: quite a bit(n=884,439)	38	24		
Baseline: very much(n=884,439)	12	2		

Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	626	315		
Week 17: a little(n=839,419)	160	80		
Week 17: quite a bit(n=839,419)	39	18		
Week 17: very much(n=839,419)	14	6		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	526	260		
Week 33: a little(n=737,341)	164	62		
Week 33: quite a bit(n=737,341)	34	15		
Week 33: very much(n=737,341)	13	4		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	444	188		
Week 49: a little(n=635,250)	138	52		
Week 49: quite a bit(n=635,250)	41	5		
Week 49: very much(n=635,250)	12	5		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	371	149		
Week 65: a little(n=536,193)	119	37		
Week 65: quite a bit(n=536,193)	31	7		
Week 65: very much(n=536,193)	15	0		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	306	115		
Week 81: a little(n=434,148)	84	26		
Week 81: quite a bit(n=434,148)	34	6		
Week 81: very much(n=434,148)	10	1		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	239	80		
Week 97: a little(n=365,95)	92	13		
Week 97: quite a bit(n=365,95)	30	1		
Week 97: very much(n=365,95)	4	1		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	190	55		
Week 113: a little(n=275,73)	62	12		
Week 113: quite a bit(n=275,73)	19	5		
Week 113: very much(n=275,73)	4	1		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	128	30		
Week 129: a little(n=192,41)	51	8		
Week 129: quite a bit(n=192,41)	9	3		
Week 129: very much(n=192,41)	4	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	78	17		
Week 145: a little(n=116,21)	29	3		
Week 145: quite a bit(n=116,21)	7	1		
Week 145: very much(n=116,21)	2	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	26	4		
Week 161: a little(n=40,8)	11	3		
Week 161: quite a bit(n=40,8)	1	0		
Week 161: very much(n=40,8)	2	1		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	2	0		

Week 177: a little(n=6,1)	2	1		
Week 177: quite a bit(n=6,1)	2	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 46

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 46 ^[41]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 46 are reported. Question 46 was following: "Have you had swelling in your legs or ankles?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	663	323		
Baseline: a little(n=884,439)	189	89		
Baseline: quite a bit(n=884,439)	22	22		
Baseline: very much(n=884,439)	10	5		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	625	284		
Week 17: a little(n=839,419)	179	112		
Week 17: quite a bit(n=839,419)	30	21		
Week 17: very much(n=839,419)	5	2		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	530	243		
Week 33: a little(n=737,341)	159	76		
Week 33: quite a bit(n=737,341)	41	20		
Week 33: very much(n=737,341)	7	2		

Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	453	176		
Week 49: a little(n=635,250)	155	58		
Week 49: quite a bit(n=635,250)	23	15		
Week 49: very much(n=635,250)	4	1		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	378	135		
Week 65: a little(n=536,193)	127	48		
Week 65: quite a bit(n=536,193)	27	10		
Week 65: very much(n=536,193)	4	0		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	301	104		
Week 81: a little(n=434,148)	102	36		
Week 81: quite a bit(n=434,148)	27	7		
Week 81: very much(n=434,148)	4	1		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	259	69		
Week 97: a little(n=365,95)	79	20		
Week 97: quite a bit(n=365,95)	19	5		
Week 97: very much(n=365,95)	8	1		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	191	40		
Week 113: a little(n=275,73)	65	27		
Week 113: quite a bit(n=275,73)	16	6		
Week 113: very much(n=275,73)	3	0		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	134	27		
Week 129: a little(n=192,41)	48	14		
Week 129: quite a bit(n=192,41)	8	0		
Week 129: very much(n=192,41)	2	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	76	15		
Week 145: a little(n=116,21)	34	5		
Week 145: quite a bit(n=116,21)	5	1		
Week 145: very much(n=116,21)	1	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	31	6		
Week 161: a little(n=40,8)	8	2		
Week 161: quite a bit(n=40,8)	1	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	3	0		
Week 177: a little(n=6,1)	3	0		
Week 177: quite a bit(n=6,1)	0	1		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 47

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 47 ^[42]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 47 are reported. Question 47 was following: "Has weight loss been a problem for you?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145, 161 and 177

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	820	399		
Baseline: a little(n=884,439)	48	25		
Baseline: quite a bit(n=884,439)	10	10		
Baseline: very much(n=884,439)	6	5		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	733	375		
Week 17: a little(n=839,419)	81	28		
Week 17: quite a bit(n=839,419)	15	13		
Week 17: very much(n=839,419)	10	3		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	643	296		
Week 33: a little(n=737,341)	72	35		
Week 33: quite a bit(n=737,341)	13	5		
Week 33: very much(n=737,341)	9	5		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	553	215		
Week 49: a little(n=635,250)	61	29		
Week 49: quite a bit(n=635,250)	15	3		
Week 49: very much(n=635,250)	6	3		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	479	168		
Week 65: a little(n=536,193)	39	20		
Week 65: quite a bit(n=536,193)	11	4		

Week 65: very much(n=536,193)	7	1		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	371	136		
Week 81: a little(n=434,148)	46	10		
Week 81: quite a bit(n=434,148)	14	1		
Week 81: very much(n=434,148)	3	1		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	314	84		
Week 97: a little(n=365,95)	36	10		
Week 97: quite a bit(n=365,95)	10	0		
Week 97: very much(n=365,95)	5	1		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	235	62		
Week 113: a little(n=275,73)	27	8		
Week 113: quite a bit(n=275,73)	9	1		
Week 113: very much(n=275,73)	4	2		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	169	37		
Week 129: a little(n=192,41)	17	4		
Week 129: quite a bit(n=192,41)	5	0		
Week 129: very much(n=192,41)	1	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	95	20		
Week 145: a little(n=116,21)	17	1		
Week 145: quite a bit(n=116,21)	4	0		
Week 145: very much(n=116,21)	0	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	34	8		
Week 161: a little(n=40,8)	5	0		
Week 161: quite a bit(n=40,8)	1	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	5	1		
Week 177: a little(n=6,1)	0	0		
Week 177: quite a bit(n=6,1)	1	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 48

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 48 ^[43]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 48 are reported. Question 48 was following: "Has weight gain been a problem for you?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	677	315		
Baseline: a little(n=884,439)	153	95		
Baseline: quite a bit(n=884,439)	40	16		
Baseline: very much(n=884,439)	14	13		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	674	316		
Week 17: a little(n=839,419)	118	74		
Week 17: quite a bit(n=839,419)	30	19		
Week 17: very much(n=839,419)	17	10		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	570	259		
Week 33: a little(n=737,341)	133	59		
Week 33: quite a bit(n=737,341)	21	18		
Week 33: very much(n=737,341)	13	5		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	479	193		
Week 49: a little(n=635,250)	125	44		
Week 49: quite a bit(n=635,250)	18	10		
Week 49: very much(n=635,250)	13	3		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	410	155		
Week 65: a little(n=536,193)	92	27		
Week 65: quite a bit(n=536,193)	26	9		
Week 65: very much(n=536,193)	8	2		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	327	115		
Week 81: a little(n=434,148)	71	27		
Week 81: quite a bit(n=434,148)	28	5		
Week 81: very much(n=434,148)	8	1		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	267	76		

Week 97: a little(n=365,95)	70	16		
Week 97: quite a bit(n=365,95)	24	2		
Week 97: very much(n=365,95)	4	1		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	200	60		
Week 113: a little(n=275,73)	56	10		
Week 113: quite a bit(n=275,73)	10	3		
Week 113: very much(n=275,73)	9	0		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	156	32		
Week 129: a little(n=192,41)	27	8		
Week 129: quite a bit(n=192,41)	5	1		
Week 129: very much(n=192,41)	4	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	89	16		
Week 145: a little(n=116,21)	18	5		
Week 145: quite a bit(n=116,21)	7	0		
Week 145: very much(n=116,21)	2	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	31	6		
Week 161: a little(n=40,8)	6	2		
Week 161: quite a bit(n=40,8)	1	0		
Week 161: very much(n=40,8)	2	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	2	0		
Week 177: a little(n=6,1)	3	1		
Week 177: quite a bit(n=6,1)	1	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 49

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 49 ^[44]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 49 are reported. Question 49 was following: "Have you felt less masculine as a result of your illness or treatment?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	435	214		
Baseline: a little(n=884,439)	234	131		
Baseline: quite a bit(n=884,439)	138	59		
Baseline: very much(n=884,439)	77	35		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	400	210		
Week 17: a little(n=839,419)	244	115		
Week 17: quite a bit(n=839,419)	109	57		
Week 17: very much(n=839,419)	86	37		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	345	167		
Week 33: a little(n=737,341)	207	107		
Week 33: quite a bit(n=737,341)	109	38		
Week 33: very much(n=737,341)	76	29		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	302	127		
Week 49: a little(n=635,250)	187	68		
Week 49: quite a bit(n=635,250)	84	36		
Week 49: very much(n=635,250)	62	19		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	263	90		
Week 65: a little(n=536,193)	142	57		
Week 65: quite a bit(n=536,193)	71	24		
Week 65: very much(n=536,193)	60	22		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	206	74		
Week 81: a little(n=434,148)	124	38		
Week 81: quite a bit(n=434,148)	57	17		
Week 81: very much(n=434,148)	47	19		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	175	46		
Week 97: a little(n=365,95)	98	28		
Week 97: quite a bit(n=365,95)	47	10		
Week 97: very much(n=365,95)	45	11		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	136	31		
Week 113: a little(n=275,73)	78	27		
Week 113: quite a bit(n=275,73)	30	8		
Week 113: very much(n=275,73)	31	7		
Week 113: not answered(n=275,73)	0	0		

Week 129: not at all(n=192,41)	91	18		
Week 129: a little(n=192,41)	49	16		
Week 129: quite a bit(n=192,41)	27	5		
Week 129: very much(n=192,41)	25	2		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	59	9		
Week 145: a little(n=116,21)	31	9		
Week 145: quite a bit(n=116,21)	18	1		
Week 145: very much(n=116,21)	8	2		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	18	2		
Week 161: a little(n=40,8)	15	3		
Week 161: quite a bit(n=40,8)	3	1		
Week 161: very much(n=40,8)	4	2		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	3	0		
Week 177: a little(n=6,1)	3	1		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 50

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 50 ^[45]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 50 are reported. Question 50 was following: "To what extent were you interested in sex?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	586	291		
Baseline: a little(n=884,439)	204	101		
Baseline: quite a bit(n=884,439)	67	32		
Baseline: very much(n=884,439)	27	15		
Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	637	293		
Week 17: a little(n=839,419)	136	92		
Week 17: quite a bit(n=839,419)	45	20		
Week 17: very much(n=839,419)	21	14		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	542	251		
Week 33: a little(n=737,341)	136	66		
Week 33: quite a bit(n=737,341)	37	18		
Week 33: very much(n=737,341)	22	6		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	483	180		
Week 49: a little(n=635,250)	106	50		
Week 49: quite a bit(n=635,250)	33	12		
Week 49: very much(n=635,250)	13	8		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	417	143		
Week 65: a little(n=536,193)	78	37		
Week 65: quite a bit(n=536,193)	27	9		
Week 65: very much(n=536,193)	14	4		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	320	114		
Week 81: a little(n=434,148)	76	24		
Week 81: quite a bit(n=434,148)	26	9		
Week 81: very much(n=434,148)	12	1		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	286	65		
Week 97: a little(n=365,95)	52	19		
Week 97: quite a bit(n=365,95)	20	8		
Week 97: very much(n=365,95)	7	3		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	218	59		
Week 113: a little(n=275,73)	36	11		
Week 113: quite a bit(n=275,73)	14	1		
Week 113: very much(n=275,73)	7	2		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	156	33		
Week 129: a little(n=192,41)	24	6		
Week 129: quite a bit(n=192,41)	9	2		
Week 129: very much(n=192,41)	3	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	92	14		
Week 145: a little(n=116,21)	16	3		

Week 145: quite a bit(n=116,21)	7	4		
Week 145: very much(n=116,21)	1	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	30	5		
Week 161: a little(n=40,8)	5	2		
Week 161: quite a bit(n=40,8)	4	1		
Week 161: very much(n=40,8)	1	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	4	1		
Week 177: a little(n=6,1)	1	0		
Week 177: quite a bit(n=6,1)	1	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 51

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 51 ^[46]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 51 are reported. Question 51 was following: "To what extent were you sexually active (with or without intercourse)?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=884,439)	735	374		
Baseline: a little(n=884,439)	98	38		
Baseline: quite a bit(n=884,439)	41	19		
Baseline: very much(n=884,439)	10	8		

Baseline: not answered(n=884,439)	0	0		
Week 17: not at all(n=839,419)	734	354		
Week 17: a little(n=839,419)	71	44		
Week 17: quite a bit(n=839,419)	24	13		
Week 17: very much(n=839,419)	10	8		
Week 17: not answered(n=839,419)	0	0		
Week 33: not at all(n=737,341)	642	299		
Week 33: a little(n=737,341)	68	28		
Week 33: quite a bit(n=737,341)	20	9		
Week 33: very much(n=737,341)	7	5		
Week 33: not answered(n=737,341)	0	0		
Week 49: not at all(n=635,250)	569	214		
Week 49: a little(n=635,250)	46	26		
Week 49: quite a bit(n=635,250)	15	6		
Week 49: very much(n=635,250)	5	4		
Week 49: not answered(n=635,250)	0	0		
Week 65: not at all(n=536,193)	485	170		
Week 65: a little(n=536,193)	37	14		
Week 65: quite a bit(n=536,193)	12	7		
Week 65: very much(n=536,193)	2	2		
Week 65: not answered(n=536,193)	0	0		
Week 81: not at all(n=434,148)	381	130		
Week 81: a little(n=434,148)	32	13		
Week 81: quite a bit(n=434,148)	15	5		
Week 81: very much(n=434,148)	6	0		
Week 81: not answered(n=434,148)	0	0		
Week 97: not at all(n=365,95)	333	79		
Week 97: a little(n=365,95)	20	12		
Week 97: quite a bit(n=365,95)	9	4		
Week 97: very much(n=365,95)	3	0		
Week 97: not answered(n=365,95)	0	0		
Week 113: not at all(n=275,73)	250	68		
Week 113: a little(n=275,73)	16	3		
Week 113: quite a bit(n=275,73)	6	2		
Week 113: very much(n=275,73)	3	0		
Week 113: not answered(n=275,73)	0	0		
Week 129: not at all(n=192,41)	176	37		
Week 129: a little(n=192,41)	8	3		
Week 129: quite a bit(n=192,41)	5	1		
Week 129: very much(n=192,41)	3	0		
Week 129: not answered(n=192,41)	0	0		
Week 145: not at all(n=116,21)	106	17		
Week 145: a little(n=116,21)	4	3		
Week 145: quite a bit(n=116,21)	5	1		
Week 145: very much(n=116,21)	1	0		
Week 145: not answered(n=116,21)	0	0		
Week 161: not at all(n=40,8)	35	6		
Week 161: a little(n=40,8)	3	2		
Week 161: quite a bit(n=40,8)	1	0		
Week 161: very much(n=40,8)	1	0		
Week 161: not answered(n=40,8)	0	0		
Week 177: not at all(n=6,1)	5	1		

Week 177: a little(n=6,1)	0	0		
Week 177: quite a bit(n=6,1)	1	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 52

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 52 ^[47]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 52 are reported. Question 52 was following: "To what extent was sex enjoyable for you?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=50,24)	5	6		
Baseline: a little(n=50,24)	23	11		
Baseline: quite a bit(n=50,24)	14	5		
Baseline: very much(n=50,24)	8	2		
Baseline: not answered(n=50,24)	0	0		
Week 17: not at all(n=839,419)	7	3		
Week 17: a little(n=839,419)	13	9		
Week 17: quite a bit(n=839,419)	16	11		
Week 17: very much(n=839,419)	3	4		
Week 17: not answered(n=839,419)	800	392		
Week 33: not at all(n=737,341)	8	4		
Week 33: a little(n=737,341)	17	8		
Week 33: quite a bit(n=737,341)	11	5		
Week 33: very much(n=737,341)	4	0		

Week 33: not answered(n=737,341)	697	324		
Week 49: not at all(n=635,250)	3	4		
Week 49: a little(n=635,250)	6	5		
Week 49: quite a bit(n=635,250)	9	5		
Week 49: very much(n=635,250)	3	4		
Week 49: not answered(n=635,250)	614	232		
Week 65: not at all(n=536,193)	4	2		
Week 65: a little(n=536,193)	6	4		
Week 65: quite a bit(n=536,193)	9	4		
Week 65: very much(n=536,193)	3	0		
Week 65: not answered(n=536,193)	514	183		
Week 81: not at all(n=434,148)	5	2		
Week 81: a little(n=434,148)	7	3		
Week 81: quite a bit(n=434,148)	4	2		
Week 81: very much(n=434,148)	5	1		
Week 81: not answered(n=434,148)	413	140		
Week 97: not at all(n=365,95)	2	2		
Week 97: a little(n=365,95)	5	0		
Week 97: quite a bit(n=365,95)	3	3		
Week 97: very much(n=365,95)	3	0		
Week 97: not answered(n=365,95)	352	90		
Week 113: not at all(n=275,73)	0	1		
Week 113: a little(n=275,73)	5	1		
Week 113: quite a bit(n=275,73)	2	0		
Week 113: very much(n=275,73)	2	0		
Week 113: not answered(n=275,73)	266	71		
Week 129: not at all(n=192,41)	1	0		
Week 129: a little(n=192,41)	1	0		
Week 129: quite a bit(n=192,41)	1	0		
Week 129: very much(n=192,41)	1	0		
Week 129: not answered(n=192,41)	188	41		
Week 145: not at all(n=116,21)	1	0		
Week 145: a little(n=116,21)	0	0		
Week 145: quite a bit(n=116,21)	1	1		
Week 145: very much(n=116,21)	0	0		
Week 145: not answered(n=116,21)	114	20		
Week 161: not at all(n=40,8)	1	0		
Week 161: a little(n=40,8)	1	0		
Week 161: quite a bit(n=40,8)	0	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	38	8		
Week 177: not at all(n=6,1)	0	0		
Week 177: a little(n=6,1)	0	0		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	6	1		

Statistical analyses

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 53

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 53 ^[48]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 53 are reported. Question 53 was following: "Did you have difficulty getting or maintaining an erection?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145, 161 and 177

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=50,24)	6	4		
Baseline: a little(n=50,24)	19	5		
Baseline: quite a bit(n=50,24)	4	4		
Baseline: very much(n=50,24)	21	11		
Baseline: not answered(n=50,24)	0	0		
Week 17: not at all(n=839,419)	10	8		
Week 17: a little(n=884,439)	8	8		
Week 17: quite a bit(n=884,439)	8	4		
Week 17: very much(n=884,439)	13	7		
Week 17: not answered(n=884,439)	800	392		
Week 33: not at all(n=737,341)	6	2		
Week 33: a little(n=737,341)	8	6		
Week 33: quite a bit(n=737,341)	8	3		
Week 33: very much(n=737,341)	18	6		
Week 33: not answered(n=737,341)	697	324		
Week 49: not at all(n=635,250)	4	6		
Week 49: a little(n=635,250)	6	5		
Week 49: quite a bit(n=635,250)	0	1		
Week 49: very much(n=635,250)	11	6		
Week 49: not answered(n=635,250)	614	232		
Week 65: not at all(n=536,193)	3	1		
Week 65: a little(n=536,193)	4	4		

Week 65: quite a bit(n=536,193)	4	2		
Week 65: very much(n=536,193)	11	3		
Week 65: not answered(n=536,193)	514	183		
Week 81: not at all(n=434,148)	7	3		
Week 81: a little(n=434,148)	2	2		
Week 81: quite a bit(n=434,148)	3	2		
Week 81: very much(n=434,148)	9	1		
Week 81: not answered(n=434,148)	413	140		
Week 97: not at all(n=365,95)	2	1		
Week 97: a little(n=365,95)	5	1		
Week 97: quite a bit(n=365,95)	1	1		
Week 97: very much(n=365,95)	5	2		
Week 97: not answered(n=365,95)	352	90		
Week 113: not at all(n=275,73)	1	0		
Week 113: a little(n=275,73)	3	1		
Week 113: quite a bit(n=275,73)	1	0		
Week 113: very much(n=275,73)	4	1		
Week 113: not answered(n=275,73)	266	71		
Week 129: not at all(n=192,41)	0	0		
Week 129: a little(n=192,41)	1	0		
Week 129: quite a bit(n=192,41)	0	0		
Week 129: very much(n=192,41)	3	0		
Week 129: not answered(n=192,41)	188	41		
Week 145: not at all(n=116,21)	1	0		
Week 145: a little(n=116,21)	0	1		
Week 145: quite a bit(n=116,21)	0	0		
Week 145: very much(n=116,21)	1	0		
Week 145: not answered(n=116,21)	114	20		
Week 161: not at all(n=40,8)	1	0		
Week 161: a little(n=40,8)	0	0		
Week 161: quite a bit(n=40,8)	1	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	38	8		
Week 177: not at all(n=6,1)	0	0		
Week 177: a little(n=6,1)	0	0		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	6	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 54

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 54 ^[49]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 54 are reported. Question 54 was following: "Did you have ejaculation problems (e.g, dry ejaculation)?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=50,24)	11	7		
Baseline: a little(n=50,24)	14	4		
Baseline: quite a bit(n=50,24)	3	2		
Baseline: very much(n=50,24)	22	11		
Baseline: not answered(n=50,24)	0	0		
Week 17: not at all(n=839,419)	13	11		
Week 17: a little(n=839,419)	5	5		
Week 17: quite a bit(n=839,419)	3	1		
Week 17: very much(n=839,419)	18	10		
Week 17: not answered(n=839,419)	800	392		
Week 33: not at all(n=737,341)	12	10		
Week 33: a little(n=737,341)	9	1		
Week 33: quite a bit(n=737,341)	5	0		
Week 33: very much(n=737,341)	14	6		
Week 33: not answered(n=737,341)	697	324		
Week 49: not at all(n=635,250)	7	6		
Week 49: a little(n=635,250)	3	5		
Week 49: quite a bit(n=635,250)	1	1		
Week 49: very much(n=635,250)	10	6		
Week 49: not answered(n=635,250)	614	232		
Week 65: not at all(n=536,193)	8	3		
Week 65: a little(n=536,193)	2	1		
Week 65: quite a bit(n=536,193)	1	2		
Week 65: very much(n=536,193)	11	4		
Week 65: not answered(n=536,193)	514	183		
Week 81: not at all(n=434,148)	7	4		
Week 81: a little(n=434,148)	0	0		
Week 81: quite a bit(n=434,148)	3	0		
Week 81: very much(n=434,148)	11	4		
Week 81: not answered(n=434,148)	413	140		

Week 97: not at all(n=365,95)	5	2		
Week 97: a little(n=365,95)	3	0		
Week 97: quite a bit(n=365,95)	0	1		
Week 97: very much(n=365,95)	5	2		
Week 97: not answered(n=365,95)	352	90		
Week 113: not at all(n=275,73)	3	2		
Week 113: a little(n=275,73)	1	0		
Week 113: quite a bit(n=275,73)	0	0		
Week 113: very much(n=275,73)	5	0		
Week 113: not answered(n=275,73)	266	71		
Week 129: not at all(n=192,41)	1	0		
Week 129: a little(n=192,41)	0	0		
Week 129: quite a bit(n=192,41)	0	0		
Week 129: very much(n=192,41)	3	0		
Week 129: not answered(n=192,41)	188	41		
Week 145: not at all(n=116,21)	2	0		
Week 145: a little(n=116,21)	0	1		
Week 145: quite a bit(n=116,21)	0	0		
Week 145: very much(n=116,21)	0	0		
Week 145: not answered(n=116,21)	114	20		
Week 161: not at all(n=40,8)	1	0		
Week 161: a little(n=40,8)	0	0		
Week 161: quite a bit(n=40,8)	1	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	38	8		
Week 177: not at all(n=6,1)	0	0		
Week 177: a little(n=6,1)	0	0		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	6	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 55

End point title	Number of Subjects With European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) Module Score for Question 55 ^[50]
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End point description:

The EORTC QLQ-PR25, a module of the EORTC QLQ-30 questionnaire was used to assess the quality of life. It consisted of 25 questions (Question 31 to 55) distributed on 6 domains: urinary symptoms (8 items), incontinence aid (1 item), bowel symptoms (4 items), hormonal treatment-related symptoms (HTRS) (6 items), sexual activity (2 items), and sexual functioning (4 items). Subjects answered each of these questions using 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Number of subjects with various responses to the question 55 are reported. Question 55 was following: "Have you felt uncomfortable about being sexually intimate?" The ITT population was defined as all subjects randomly assigned to study treatment and was based on randomized treatment assignment regardless of whether or not treatment was administered. Here, 'n' = subjects evaluable for this end point at specified time points.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 17, 33, 49, 65, 81, 97, 113, 129, 145,161 and 177

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	933	468		
Units: subjects				
Baseline: not at all(n=50,24)	31	13		
Baseline: a little(n=50,24)	13	8		
Baseline: quite a bit(n=50,24)	4	0		
Baseline: very much(n=50,24)	2	3		
Baseline: not answered(n=50,24)	0	0		
Week 17: not at all(n=839,419)	23	14		
Week 17: a little(n=839,419)	11	7		
Week 17: quite a bit(n=839,419)	2	3		
Week 17: very much(n=839,419)	3	3		
Week 17: not answered(n=839,419)	800	392		
Week 33: not at all(n=737,341)	24	10		
Week 33: a little(n=737,341)	6	4		
Week 33: quite a bit(n=737,341)	6	2		
Week 33: very much(n=737,341)	4	1		
Week 33: not answered(n=737,341)	697	324		
Week 49: not at all(n=635,250)	16	10		
Week 49: a little(n=635,250)	4	6		
Week 49: quite a bit(n=635,250)	1	1		
Week 49: very much(n=635,250)	0	1		
Week 49: not answered(n=635,250)	614	232		
Week 65: not at all(n=536,193)	13	5		
Week 65: a little(n=536,193)	7	3		
Week 65: quite a bit(n=536,193)	1	2		
Week 65: very much(n=536,193)	1	0		
Week 65: not answered(n=536,193)	514	183		
Week 81: not at all(n=434,148)	13	5		
Week 81: a little(n=434,148)	6	1		
Week 81: quite a bit(n=434,148)	1	1		
Week 81: very much(n=434,148)	1	1		
Week 81: not answered(n=434,148)	413	140		
Week 97: not at all(n=365,95)	8	3		
Week 97: a little(n=365,95)	3	2		
Week 97: quite a bit(n=365,95)	1	0		
Week 97: very much(n=365,95)	1	0		
Week 97: not answered(n=365,95)	352	90		
Week 113: not at all(n=275,73)	7	2		
Week 113: a little(n=275,73)	0	0		
Week 113: quite a bit(n=275,73)	1	0		
Week 113: very much(n=275,73)	1	0		

Week 113: not answered(n=275,73)	266	71		
Week 129: not at all(n=192,41)	3	0		
Week 129: a little(n=192,41)	0	0		
Week 129: quite a bit(n=192,41)	1	0		
Week 129: very much(n=192,41)	0	0		
Week 129: not answered(n=192,41)	188	41		
Week 145: not at all(n=116,21)	2	1		
Week 145: a little(n=116,21)	0	0		
Week 145: quite a bit(n=116,21)	0	0		
Week 145: very much(n=116,21)	0	0		
Week 145: not answered(n=116,21)	114	20		
Week 161: not at all(n=40,8)	1	0		
Week 161: a little(n=40,8)	0	0		
Week 161: quite a bit(n=40,8)	1	0		
Week 161: very much(n=40,8)	0	0		
Week 161: not answered(n=40,8)	38	8		
Week 177: not at all(n=6,1)	0	0		
Week 177: a little(n=6,1)	0	0		
Week 177: quite a bit(n=6,1)	0	0		
Week 177: very much(n=6,1)	0	0		
Week 177: not answered(n=6,1)	6	1		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[51]
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End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. A treatment-emergent AE (TEAE) was defined as an AE that occurred from the date and time of the first dose of study drug through the date of last dose +30 days (or the day before initiation of a new antineoplastic treatment, whichever occurred first). AEs included both non-serious adverse events (AEs) and SAEs. The safety population was defined as all subjects randomly assigned to receive at least 1 dose or partial dose of study drug (enzalutamide or placebo) according to the actual treatment received (not the treatment assigned).

End point type	Secondary
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End point timeframe:

From first dose of study drug to the last dose + 30 days (or the day before initiation of a new antineoplastic treatment, whichever occurred first) (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	930	465		
Units: subjects				
AEs	808	360		
SAEs	226	85		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With Treatment-Emergent Adverse Events Greater Than or Equal to Grade 3, Based on National Cancer Institute (NCI) Common Terminology Criteria (CTC) for AEs (CTCAE), Version 4.0 ^[52]
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End point description:

AE: any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. As per NCI CTCAE, Grade 3 events = medically significant but not immediately life-threatening, unacceptable or intolerable events, significantly interrupting usual daily activity, require systemic drug therapy/other treatment, Grade 4 events = subject to be in imminent danger of death. Grade 5 events = death. A treatment-emergent AE (TEAE) was defined as an AE that occurred from the date and time of the first dose of study drug through the date of last dose +30 days (or the day before initiation of a new antineoplastic treatment, whichever occurred first). Number of subjects with AEs of any of the Grade 3 or above (Grade 4, 5) were reported. The safety population was defined as all subjects randomly assigned to receive at least 1 dose or partial dose of study drug (enzalutamide or placebo) according to the actual treatment received (not the treatment assigned).

End point type	Secondary
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End point timeframe:

From first dose of study drug to the last dose + 30 days (or the day before initiation of a new antineoplastic treatment, whichever occurred first) (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	930	465		
Units: subjects	292	109		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Discontinuations From Study Treatment Due to

Adverse Events (AEs)

End point title	Number of Subjects With Discontinuations From Study Treatment Due to Adverse Events (AEs) ^[53]
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End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both non-serious adverse events (AEs) and SAEs. The safety population was defined as all subjects randomly assigned to receive at least 1 dose or partial dose of study drug (enzalutamide or placebo) according to the actual treatment received (not the treatment assigned).

End point type	Secondary
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End point timeframe:

From first dose of study drug to the last dose + 30 days (or the day before initiation of a new antineoplastic treatment, whichever occurred first) (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	930	465		
Units: subjects	87	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Increase of 2 or More National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) (Version 4.0) Toxicity Grades Above Baseline - Hematology

End point title	Number of Subjects With Increase of 2 or More National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) (Version 4.0) Toxicity Grades Above Baseline - Hematology ^[54]
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End point description:

Hematology parameters: Haemoglobin (grams per liter [g/L]); leukocytes (log 10 raised to power 9 per liter [$10^9/L$]); lymphocytes (log 10 raised to power 6 per liter [$10^6/L$]); neutrophils (log 10 raised to power 6 per liter [$10^6/L$]); platelets (log 10 raised to power 9 per litre [$10^9/L$]). The safety population was defined as all subjects randomly assigned to receive at least 1 dose or partial dose of study drug (enzalutamide or placebo) according to the actual treatment received (not the treatment assigned).

End point type	Secondary
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End point timeframe:

From first dose of study drug to the last dose + 30 days (or the day before initiation of a new antineoplastic treatment, whichever occurred first) (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	930	465		
Units: subjects				
Haemoglobin (Low)	12	7		
Leukocytes (Low)	7	7		
Lymphocytes (High)	4	2		
Lymphocytes (Low)	44	26		
Neutrophils (Low)	13	4		
Platelets (Low)	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Increase of 2 or More National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) (Version 4.0) Toxicity Grades Above Baseline – Chemistry

End point title	Number of Subjects With Increase of 2 or More National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) (Version 4.0) Toxicity Grades Above Baseline – Chemistry ^[55]
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End point description:

Chemistry parameters: Alanine aminotransferase (units per liter [U/L]); albumin (g/L); alkaline phosphatase (U/L); bilirubin (micromoles per liter [umol/L]); calcium (millimoles per liter [mmol/L]); creatine kinase (U/L); creatinine (umol/L); glucose, magnesium, phosphate, potassium, sodium (mmol/L). The safety population was defined as all subjects randomly assigned to receive at least 1 dose or partial dose of study drug (enzalutamide or placebo) according to the actual treatment received (not the treatment assigned).

End point type	Secondary
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End point timeframe:

From first dose of study drug to the last dose + 30 days (or the day before initiation of a new antineoplastic treatment, whichever occurred first) (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	930	465		
Units: subjects				
Alanine Aminotransferase (High)	4	1		
Albumin (Low)	7	0		
Alkaline Phosphatase (High)	3	6		
Aspartate Aminotransferase (High)	3	1		
Bilirubin (High)	4	1		
Calcium (High)	1	1		
Calcium (Low)	2	1		
Creatine Kinase (High)	4	3		

Creatinine (High)	1	7		
Glucose (High)	26	8		
Glucose (Low)	5	1		
Magnesium (High)	1	0		
Magnesium (Low)	1	0		
Phosphate (Low)	30	13		
Potassium (High)	14	5		
Potassium (Low)	0	3		
Sodium (High)	2	1		
Sodium (Low)	12	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Vital Signs

End point title	Number of Subjects with Clinically Significant Vital Signs ^[56]
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End point description:

Vital signs included Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and heart rate. The safety population was defined as all subjects randomly assigned to receive at least 1 dose or partial dose of study drug (enzalutamide or placebo) according to the actual treatment received (not the treatment assigned).

End point type	Secondary
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End point timeframe:

From first dose of study drug to the last dose + 30 days (or the day before initiation of a new antineoplastic treatment, whichever occurred first) (until the data cut-off date of 28 June 2017, maximum duration of treatment: 42.8 months)

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in reporting arms: Enzalutamide 160 mg and placebo

End point values	Enzalutamide 160 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	930	465		
Units: subjects				
SBP	738	328		
DBP	563	229		
Heart rate	7	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after last dose of study drug or till death, whichever occurred first (up to a maximum duration of 69.8 months)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as SAE in 1 subject and as Non-SAE in another, or a subject may have experienced both a SA and Non-SAE. Data reported in this section was collected and analyzed only for subject who were treated with at least 1 dose of study drug.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Enzalutamide 160 mg
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Reporting group description:

Subjects received 4 capsules of Enzalutamide 40 mg each (total dose 160 mg per day) orally, once daily in double-blind and open-label phase (up to a maximum of 68.8 months) until radiographic progression. Subjects after last dose of study drug, were followed up for safety up to 30 days, and were long term followed up (for survival status and new prostate cancer therapies) from last dose to the death date or last known survival date.

Reporting group title	Placebo
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Reporting group description:

Subjects received 4 capsules of placebo (matched to Enzalutamide) orally, once daily in double blind phase (up to a maximum of 51.3 months) until radiographic progression. Subjects were given an opportunity to switch to open-label enzalutamide after completion of double blind phase. Subjects after last dose of study drug, were followed up for safety up to 30 days and were long term followed up (for survival status and new prostate cancer therapies) to the death date or last known survival date.

Reporting group title	Placebo Patients Crossover to Enzalutamide 160 mg
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Reporting group description:

Subjects who received placebo in double-blind phase and who agreed to proceed to open-label phase, received 4 capsules of Enzalutamide 40 mg each (total dose of 160 mg per day), orally once daily (up to a maximum of 18.8 months) until radiographic progression. Subjects after last dose of study drug, were followed up for safety up to 30 days and were long term followed up (for survival status and new prostate cancer therapies) to the death date or last known survival date.

Serious adverse events	Enzalutamide 160 mg	Placebo	Placebo Patients Crossover to Enzalutamide 160 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	372 / 930 (40.00%)	100 / 465 (21.51%)	12 / 87 (13.79%)
number of deaths (all causes)	285	173	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Adenocarcinoma of colon			
subjects affected / exposed	6 / 930 (0.65%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (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
Bladder neoplasm			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 papilloma			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Chronic lymphocytic leukaemia			

subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Colon cancer			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Malignant neoplasm of unknown primary site			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Mesothelioma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Metastases to bone			
subjects affected / exposed	2 / 930 (0.22%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	2 / 930 (0.22%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastases to lymph nodes			

subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Metastases to rectum			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to spine			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Metastatic neoplasm			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Neoplasm progression			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Pituitary tumour benign			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer metastatic			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Small intestine adenocarcinoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			

subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Waldenstrom's macroglobulinaemia			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Cancer Recurrent			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopharyngeal Cancer			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal Cancer Recurrent			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal Squamous Cell Carcinoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Adenocarcinoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 Cancer Metastatic			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 Melanoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer			
subjects affected / exposed	2 / 930 (0.22%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Clear cell renal cell carcinoma			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Neuroendocrine carcinoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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			
Aortic aneurysm			
subjects affected / exposed	4 / 930 (0.43%)	0 / 465 (0.00%)	0 / 87 (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
Aortic dissection			

subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Aortic stenosis			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 930 (0.11%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	5 / 930 (0.54%)	0 / 465 (0.00%)	0 / 87 (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
Ischaemia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Peripheral artery stenosis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angiopathy			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic Rupture			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive Crisis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Bladder calculus removal			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystoprostatectomy			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transurethral prostatectomy			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic Operation			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	7 / 930 (0.75%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Disease progression			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 1
Fatigue			

subjects affected / exposed	4 / 930 (0.43%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (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
Oedema peripheral			
subjects affected / exposed	0 / 930 (0.00%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Pyrexia			
subjects affected / exposed	3 / 930 (0.32%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 5	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent-graft endoleak			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Vessel puncture site haematoma			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance Status Decreased			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Cardiac Death			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Swelling			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic shock			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Iodine allergy			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Benign prostatic hyperplasia			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Penile pain			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Prostatic cyst			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Prostatic haemorrhage			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Prostatic obstruction			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Prostatomegaly			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Prostatitis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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

Choking			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Dyspnoea			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Interstitial lung disease			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Laryngeal oedema			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Pleural effusion			
subjects affected / exposed	4 / 930 (0.43%)	0 / 465 (0.00%)	0 / 87 (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
Pleurisy			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Pneumonia aspiration			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Pulmonary embolism			

subjects affected / exposed	4 / 930 (0.43%)	3 / 465 (0.65%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 5	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 Disorder			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Oedema			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Depression			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Mania			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Alcohol Abuse			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional State			
subjects affected / exposed	0 / 930 (0.00%)	0 / 465 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Blood creatinine increased			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure decreased			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 urea increased			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Haemoglobin decreased			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Clavicle fracture			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Comminuted fracture			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Concussion			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis radiation			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Excoriation			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	12 / 930 (1.29%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	3 / 15	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	6 / 930 (0.65%)	0 / 465 (0.00%)	0 / 87 (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
Femur fracture			

subjects affected / exposed	5 / 930 (0.54%)	1 / 465 (0.22%)	0 / 87 (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
Fibula fracture			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Fracture			
subjects affected / exposed	4 / 930 (0.43%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heat stroke			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (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
Humerus fracture			
subjects affected / exposed	3 / 930 (0.32%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	3 / 930 (0.32%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (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
Pelvic fracture			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Pubis fracture			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Radius fracture			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	2 / 930 (0.22%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Subdural haematoma			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			

subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Tibia fracture			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Ulna fracture			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Urostomy complication			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Venous injury			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Vertebral Fracture			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chemical Cystitis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial Bones Fracture			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 930 (0.00%)	0 / 465 (0.00%)	1 / 87 (1.15%)
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	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (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
Thoracic Vertebral Fracture			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Toxicity To Various Agents			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Phimosi			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	6 / 930 (0.65%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	10 / 930 (1.08%)	2 / 465 (0.43%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	1 / 12	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1

Angina pectoris			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (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
Angina unstable			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (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
Aortic valve incompetence			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Arrhythmia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	9 / 930 (0.97%)	3 / 465 (0.65%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 10	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Atrioventricular block complete			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			

subjects affected / exposed	2 / 930 (0.22%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	10 / 930 (1.08%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	2 / 10	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Conduction disorder			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	8 / 930 (0.86%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Mitral valve incompetence			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Myocardial infarction			

subjects affected / exposed	10 / 930 (1.08%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 6	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	2 / 930 (0.22%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Sick sinus syndrome			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Sinus bradycardia			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Ventricular arrhythmia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Atrioventricular Block Second Degree			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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 Aneurysm			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 Failure Congestive			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Cardiogenic Shock			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiovascular Insufficiency			
subjects affected / exposed	0 / 930 (0.00%)	0 / 465 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Left Ventricular Dysfunction			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Arrest			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid Valve Disease			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Tachycardia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 Failure Acute			
subjects affected / exposed	0 / 930 (0.00%)	0 / 465 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery occlusion			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 haemorrhage			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	4 / 930 (0.43%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 930 (0.00%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	7 / 930 (0.75%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	3 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Cranial nerve disorder			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplegia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Grand mal convulsion			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	6 / 930 (0.65%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lacunar infarction			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Lethargy			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Loss of consciousness			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (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
Spinal cord compression			
subjects affected / exposed	3 / 930 (0.32%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	7 / 930 (0.75%)	2 / 465 (0.43%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	2 / 7	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	5 / 930 (0.54%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	4 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal Ganglia Haemorrhage			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Haemorrhagic Stroke			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Headache			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Radiculopathy			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Neuralgia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo Cns Origin			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	10 / 930 (1.08%)	1 / 465 (0.22%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	2 / 13	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Anaemia macrocytic			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Thrombocytopenia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Neutropenia			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Normochromic Normocytic Anaemia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Splenic Haemorrhage			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 disorders			
Abdominal hernia			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Acquired oesophageal web			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Diarrhoea			
subjects affected / exposed	2 / 930 (0.22%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal stenosis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 haemorrhage			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Dysphagia			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Faecaloma			
subjects affected / exposed	1 / 930 (0.11%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal mucosal disorder			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	3 / 930 (0.32%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	4 / 930 (0.43%)	3 / 465 (0.65%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal congestion			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Intestinal ischaemia			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 intestinal stenosis			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Melaena			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Nausea			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Peptic ulcer			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer haemorrhage			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Pharyngo-oesophageal diverticulum			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 intestinal haemorrhage			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Distension			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Colitis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic Pseudo-Obstruction			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 Necrosis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia Strangulated			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periproctitis			
subjects affected / exposed	0 / 930 (0.00%)	0 / 465 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Haemorrhage			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Volvulus			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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			
Cholangitis acute			

subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Cholecystitis			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Cholecystitis acute			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Cholelithiasis			
subjects affected / exposed	4 / 930 (0.43%)	0 / 465 (0.00%)	0 / 87 (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
Hepatic cirrhosis			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Hepatic failure			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Bile Duct Stone			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Biliary Colic			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis Obstructive			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Bladder disorder			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder hypertrophy			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 obstruction			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder outlet obstruction			
subjects affected / exposed	1 / 930 (0.11%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	2 / 930 (0.22%)	2 / 465 (0.43%)	0 / 87 (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
Calculus ureteric			

subjects affected / exposed	3 / 930 (0.32%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis haemorrhagic			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis noninfective			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Haematuria			
subjects affected / exposed	31 / 930 (3.33%)	15 / 465 (3.23%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	3 / 40	0 / 22	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	5 / 930 (0.54%)	3 / 465 (0.65%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	1 / 5	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertonic bladder			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	5 / 930 (0.54%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive uropathy			
subjects affected / exposed	0 / 930 (0.00%)	3 / 465 (0.65%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postrenal failure			

subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	2 / 930 (0.22%)	2 / 465 (0.43%)	0 / 87 (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
Renal failure			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	7 / 930 (0.75%)	8 / 465 (1.72%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure chronic			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Renal impairment			
subjects affected / exposed	1 / 930 (0.11%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal pain			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Ureteric obstruction			
subjects affected / exposed	2 / 930 (0.22%)	2 / 465 (0.43%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			

subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Urethral obstruction			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	1 / 930 (0.11%)	3 / 465 (0.65%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary fistula			
subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	3 / 930 (0.32%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	13 / 930 (1.40%)	12 / 465 (2.58%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 19	3 / 13	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	4 / 930 (0.43%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vesical fistula			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Anuria			

subjects affected / exposed	0 / 930 (0.00%)	0 / 465 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress Urinary Incontinence			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 Bladder Haemorrhage			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Disorder			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	4 / 930 (0.43%)	0 / 465 (0.00%)	0 / 87 (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
Back pain			
subjects affected / exposed	1 / 930 (0.11%)	3 / 465 (0.65%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Cervical spinal stenosis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Flank pain			

subjects affected / exposed	1 / 930 (0.11%)	1 / 465 (0.22%)	0 / 87 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Muscular weakness			
subjects affected / exposed	2 / 930 (0.22%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	5 / 930 (0.54%)	3 / 465 (0.65%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			

subjects affected / exposed	2 / 930 (0.22%)	1 / 465 (0.22%)	0 / 87 (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
Rheumatoid arthritis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Rotator cuff syndrome			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Osteoporotic fracture			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain In Extremity			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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			
Appendicitis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Bronchopneumonia			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Cellulitis			
subjects affected / exposed	6 / 930 (0.65%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	2 / 930 (0.22%)	1 / 465 (0.22%)	0 / 87 (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
Herpes zoster			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Lower respiratory tract infection			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Lung infection			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (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
Pneumonia			
subjects affected / exposed	20 / 930 (2.15%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 23	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Respiratory tract infection			

subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Septic shock			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	2 / 930 (0.22%)	0 / 465 (0.00%)	0 / 87 (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
Small intestine gangrene			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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
Soft tissue infection			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Tracheobronchitis			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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	11 / 930 (1.18%)	6 / 465 (1.29%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 11	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	9 / 930 (0.97%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 9	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral diarrhoea			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Sepsis			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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 Related Infection			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Diarrhoea Infectious			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar Pneumonia			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nail Bed Infection			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar Abscess			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 930 (0.00%)	2 / 465 (0.43%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	6 / 930 (0.65%)	0 / 465 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tooth Infection			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (0.00%)
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			
Dehydration			
subjects affected / exposed	4 / 930 (0.43%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemochromatosis			

subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Hyperkalaemia			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (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
Hyponatraemia			
subjects affected / exposed	3 / 930 (0.32%)	0 / 465 (0.00%)	0 / 87 (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
Decreased Appetite			
subjects affected / exposed	0 / 930 (0.00%)	1 / 465 (0.22%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 Diabetes Mellitus			
subjects affected / exposed	1 / 930 (0.11%)	0 / 465 (0.00%)	0 / 87 (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

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

Non-serious adverse events	Enzalutamide 160 mg	Placebo	Placebo Patients Crossover to Enzalutamide 160 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	762 / 930 (81.94%)	299 / 465 (64.30%)	45 / 87 (51.72%)
Vascular disorders			
Hot flush			
subjects affected / exposed	132 / 930 (14.19%)	38 / 465 (8.17%)	3 / 87 (3.45%)
occurrences (all)	151	40	3
Hypertension			
subjects affected / exposed	158 / 930 (16.99%)	27 / 465 (5.81%)	6 / 87 (6.90%)
occurrences (all)	214	34	6
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	93 / 930 (10.00%)	32 / 465 (6.88%)	10 / 87 (11.49%)
occurrences (all)	170	36	13
Fatigue			
subjects affected / exposed	344 / 930 (36.99%)	72 / 465 (15.48%)	13 / 87 (14.94%)
occurrences (all)	513	80	13
Oedema Peripheral			
subjects affected / exposed	59 / 930 (6.34%)	23 / 465 (4.95%)	4 / 87 (4.60%)
occurrences (all)	74	25	5
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	47 / 930 (5.05%)	15 / 465 (3.23%)	1 / 87 (1.15%)
occurrences (all)	55	19	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	54 / 930 (5.81%)	16 / 465 (3.44%)	2 / 87 (2.30%)
occurrences (all)	60	18	2
Investigations			
Weight decreased			
subjects affected / exposed	80 / 930 (8.60%)	11 / 465 (2.37%)	4 / 87 (4.60%)
occurrences (all)	93	11	5
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	159 / 930 (17.10%)	24 / 465 (5.16%)	2 / 87 (2.30%)
occurrences (all)	223	25	2
Rib Fracture			
subjects affected / exposed	63 / 930 (6.77%)	6 / 465 (1.29%)	1 / 87 (1.15%)
occurrences (all)	76	7	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	112 / 930 (12.04%)	27 / 465 (5.81%)	6 / 87 (6.90%)
occurrences (all)	138	35	6
Headache			
subjects affected / exposed	102 / 930 (10.97%)	23 / 465 (4.95%)	3 / 87 (3.45%)
occurrences (all)	122	28	3
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	60 / 930 (6.45%) 85	19 / 465 (4.09%) 30	6 / 87 (6.90%) 6
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	120 / 930 (12.90%) 145	39 / 465 (8.39%) 43	1 / 87 (1.15%) 1
Nausea subjects affected / exposed occurrences (all)	123 / 930 (13.23%) 160	42 / 465 (9.03%) 48	3 / 87 (3.45%) 3
Diarrhoea subjects affected / exposed occurrences (all)	110 / 930 (11.83%) 137	63 / 465 (13.55%) 46	3 / 87 (3.45%) 5
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	79 / 930 (8.49%) 113	33 / 465 (7.10%) 42	2 / 87 (2.30%) 2
Urinary retention subjects affected / exposed occurrences (all)	37 / 930 (3.98%) 43	31 / 465 (6.67%) 37	0 / 87 (0.00%) 0
Pollakiuria subjects affected / exposed occurrences (all)	43 / 930 (4.62%) 44	25 / 465 (5.38%) 28	0 / 87 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	118 / 930 (12.69%) 145	36 / 465 (7.74%) 48	3 / 87 (3.45%) 3
Back pain subjects affected / exposed occurrences (all)	119 / 930 (12.80%) 139	38 / 465 (8.17%) 38	4 / 87 (4.60%) 4
Musculoskeletal Pain subjects affected / exposed occurrences (all)	61 / 930 (6.56%) 72	15 / 465 (3.23%) 18	1 / 87 (1.15%) 1
Pain In Extremity subjects affected / exposed occurrences (all)	56 / 930 (6.02%) 64	15 / 465 (3.23%) 15	2 / 87 (2.30%) 2

Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	63 / 930 (6.77%) 82	28 / 465 (6.02%) 34	1 / 87 (1.15%) 1
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	108 / 930 (11.61%) 138	22 / 465 (4.73%) 24	3 / 87 (3.45%) 3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2013	Requirement for continuing the use of BTAs for bone health during the study for subjects who received prior bisphosphonates or denosumab 4 weeks before enrollment was clarified. Rationale for why progression did not mandate discontinuation of study drug; information on the method for calculating PSA DT, rationale for allowing the use of concomitant medications that lowered the seizure threshold was provided. Determination of radiographic events for the primary efficacy endpoint analysis was clarified. Additionally, the acronym for the clinical trial name was added to the study title.
31 May 2017	The timing and plan for the analyses of the primary endpoint of MFS, as well as the secondary endpoints, based on results from the nonmetastatic CRPC subgroup in the Phase 2 study MDV3100-09 and outcomes of 2 other controlled studies of enzalutamide in chemotherapy-naïve metastatic CRPC (MDV3100-03 and 9785-CL-0222) was revised. Medivation, Inc. became a wholly owned subsidiary of Pfizer Inc as of 28 September 2016. Medivation/Pfizer remained the Sponsor and the responsibility for expedited and periodic safety reporting was transferred to Pfizer Inc from ProductLife.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported