Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Efficacy and Safety of Enzalutamide in Combination With Exemestane in Patients With Advanced Breast Cancer That Is Estrogen or Progesterone Receptor-Positive and HER2-Normal

Summary

EudraCT number	2013-002717-35
Trial protocol	IE BE GB IT ES
Global end of trial date	

Results information

Result version number	v3 (current)
This version publication date	23 December 2018
First version publication date	14 October 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MDV3100-12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02007512
WHO universal trial number (UTN)	-

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 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, 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	07 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the benefit of exemestane plus enzalutamide versus exemestane plus placebo as assessed by progression-free survival (PFS) in subjects with advanced breast cancer that was estrogen or progesterone receptor-positive or both (ER+/PgR+), human epidermal growth factor receptor 2 (HER2) - normal and the subset that was also diagnostic-positive (Dx+) as followed: • Cohort 1: Subjects who had not previously received hormone treatment for advanced breast cancer • Cohort 2: Subjects who previously progressed following 1 (one) hormone treatment for advanced breast cancer

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 trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 119
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Ireland: 16
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	United Kingdom: 15
Worldwide total number of subjects	247
EEA total number of subjects	124

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	151
From 65 to 84 years	92
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a phase 2, randomized, double blind, placebo-controlled study. The results disclosed in this draft were based on the data collected till 23 Sep 2016.

Period 1

Period 1 title	Double Blind Treatment 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?	Yes
Arm title	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg

Arm description:

Subjects with no previous hormonal treatment for advanced breast cancer, received enzalutamide 160 milligram (mg) along with exemestane 50 mg, orally, once daily until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

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

Dosage and administration details:

Enzalutamide 160 mg was administered orally, once daily.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Exemestane 50 mg was administered orally, once daily.

Arm title	Cohort 1: Placebo + Exemestane 25 mg

Arm description:

Subjects with no previous hormonal treatment for advanced breast cancer received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to enzalutamide was administered orally, once daily.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Exemestane 25 mg was administered orally, once daily.

Arm title	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg

Arm description:

Subjects with previous disease progression following hormonal treatment for advanced breast cancer, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

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

Dosage and administration details:

Exemestane 50 mg was administered orally, once daily.

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

Dosage and administration details:

Enzalutamide 160 mg was administered orally, once daily.

Arm title	Cohort 2: Placebo + Exemestane 25 mg

Arm description:

Subjects with previous disease progression following hormonal treatment for advanced breast cancer, received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

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

Dosage and administration details:

Exemestane 25 mg was administered orally, once daily.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to enzalutamide was administered orally, once daily.

Number of subjects in period 1	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg
Started	63	64	60
Completed	45	49	45
Not completed	18	15	15
Consent withdrawn by subject	4	2	3
Ongoing as of the data cutoff date (23 Sep 2016)	10	11	5
Adverse event	4	2	6
Unspecified	-	-	1
Protocol deviation	-	-	-

Number of subjects in period 1	Cohort 2: Placebo + Exemestane 25 mg
Started	60
Completed	51
Not completed	9
Consent withdrawn by subject	3
Ongoing as of the data cutoff date (23 Sep 2016)	1
Adverse event	2
Unspecified	2
Protocol deviation	1

Period 2

Period 2 title	Open Label Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Cohort 1: Placebo + Exemestane 25 mg

Arm description:

Subjects with no previous hormonal treatment for advanced breast cancer received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

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

Dosage and administration details:

Enzalutamide 160 mg was administered orally, once daily

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Exemestane 50 mg was administered orally, once daily.

Arm title	Cohort 2: Placebo + Exemestane 25 mg

Arm description:

Subjects with previous disease progression following hormonal treatment for advanced breast cancer received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

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

Dosage and administration details:

Exemestane 50 mg was administered orally, once daily.

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

Dosage and administration details:

Enzalutamide 160 mg was administered orally, once daily

Number of subjects in period 2[1]	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Placebo + Exemestane 25 mg
Started	21	12
Treated	21	12
Completed	17	11
Not completed	4	1
Ongoing as of the data cutoff date (23 Sep 2016)	3	-
Adverse event	1	-
Unspecified	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: From ''double blind'' period, only eligible participants of ''Placebo + Exemestane 25 mg'' reporting arm entered into the ''open label'' period.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg
Reporting group description:	
Subjects with no previous hormonal treatment for advanced breast cancer, received enzalutamide 160 milligram (mg) along with exemestane 50 mg, orally, once daily until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.	
Reporting group title	Cohort 1: Placebo + Exemestane 25 mg
Reporting group description:	
Subjects with no previous hormonal treatment for advanced breast cancer received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.	
Reporting group title	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg
Reporting group description:	
Subjects with previous disease progression following hormonal treatment for advanced breast cancer, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.	
Reporting group title	Cohort 2: Placebo + Exemestane 25 mg
Reporting group description:	
Subjects with previous disease progression following hormonal treatment for advanced breast cancer, received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.	

Reporting group values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg
Number of subjects	63	64	60
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	32	37
From 65-84 years	20	31	23
85 years and over	1	1	0
Age continuous Units: years			
arithmetic mean	59.0	63.5	60.1

standard deviation	± 10.82	± 11.56	± 11.27

Gender, Male/Female Units: Subjects			
Female	63	64	60
Male	0	0	0

Reporting group values	Cohort 2: Placebo + Exemestane 25 mg	Total	
Number of subjects	60	247	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	40	151	
From 65-84 years	18	92	
85 years and over	2	4	
Age continuous Units: years			
arithmetic mean	60.6		
standard deviation	± 13.47	-	
Gender, Male/Female Units: Subjects			
Female	60	247	
Male	0	0	

End points

End points reporting groups

Reporting group title	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg

Reporting group description:

Subjects with no previous hormonal treatment for advanced breast cancer, received enzalutamide 160 milligram (mg) along with exemestane 50 mg, orally, once daily until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Cohort 1: Placebo + Exemestane 25 mg

Reporting group description:

Subjects with no previous hormonal treatment for advanced breast cancer received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg

Reporting group description:

Subjects with previous disease progression following hormonal treatment for advanced breast cancer, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Cohort 2: Placebo + Exemestane 25 mg

Reporting group description:

Subjects with previous disease progression following hormonal treatment for advanced breast cancer, received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Cohort 1: Placebo + Exemestane 25 mg

Reporting group description:

Subjects with no previous hormonal treatment for advanced breast cancer received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Cohort 2: Placebo + Exemestane 25 mg

Reporting group description:

Subjects with previous disease progression following hormonal treatment for advanced breast cancer received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Subject analysis set title	Enzalutamide 160 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received enzalutamide 160 mg dose orally, once daily, either in double blind treatment period or in open label treatment period until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after the last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Subject analysis set title	Exemestane 25 mg

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received exemestane 25 mg dose orally, once daily, in double blind treatment period until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after the last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Subject analysis set title	Exemestane 50 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received exemestane 50 mg dose orally, once daily until disease progression or permanent treatment discontinuation, either in double blind treatment period or in open label treatment period. Subjects were followed-up until 30 days after the last dose of study drug, the date of death, or before initiation of a new antitumor treatment, whichever occurred first.

Subject analysis set title	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg (EDC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with no previous hormonal treatment for advanced breast cancer, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Subject analysis set title	Cohort 1: Placebo + Exemestane 25 mg (EDC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with no previous hormonal treatment for advanced breast cancer received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Subject analysis set title	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg (EDC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with previous disease progression following hormonal treatment for advanced breast cancer, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Subject analysis set title	Cohort 2: Placebo + Exemestane 25 mg (EDC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with previous disease progression following hormonal treatment for advanced breast cancer, received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Primary: Progression Free Survival (PFS): Intent-to-Treat (ITT) Population By Interactive Web Recognition System (IWRS)

End point title	Progression Free Survival (PFS): Intent-to-Treat (ITT) Population By Interactive Web Recognition System (IWRS)

End point description:

PFS was defined as the time in months from randomization to the first documentation of progression of disease (PD) or death on study due to any cause, whichever occurred first. PD according to response evaluation criteria in solid tumors version 1.1 (RECIST 1.1) was defined as greater than or equal to (>=) 20 percent (%) increase in the sum of diameters of the target lesions taking as a reference the smallest sum recorded since the start of treatment or unequivocal progression in non-target lesions or the appearance of 1 or more new lesions. The analysis of PFS was based on investigator assessment of disease progression. Subjects who were not known to have had a PFS event at the analysis date were

censored at last tumor assessment date prior to data cutoff or date of new treatment initiation, whichever occurred first. Intent-to-treat (ITT) population included all the subjects randomly assigned to double-blind study treatment.

End point type	Primary

End point timeframe:

From randomization until PD, last tumor assessment without PD before new antitumor treatment initiation or death due to any cause, whichever occurred first (up to the data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	60	60
Units: months				
median (confidence interval 95%)	11.8 (7.3 to 15.9)	5.8 (3.5 to 10.9)	3.6 (1.9 to 5.5)	3.9 (2.6 to 5.4)

Statistical analyses

Statistical analysis title	Cohort 1 (Experimental versus Placebo)
Statistical analysis description:	
Hazard ratio was based on stratified Cox regression model.	
Comparison groups	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg v Cohort 1: Placebo + Exemestane 25 mg
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3631
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.535
upper limit	1.257

Statistical analysis title	Cohort 2 (Experimental versus Placebo)
Statistical analysis description:	
Hazard ratio was based on stratified Cox regression model.	
Comparison groups	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg v Cohort 2: Placebo + Exemestane 25 mg

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9212
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.659
upper limit	1.586

Primary: Progression Free Survival (PFS): Diagnostic Positive (DX+) Population By Interactive Web Recognition System (IWRS)

End point title	Progression Free Survival (PFS): Diagnostic Positive (DX+) Population By Interactive Web Recognition System (IWRS)

End point description:

PFS: time in months from randomization to first documentation of PD or death on study due to any cause, whichever occurred first. PD (as per RECIST 1.1): >= 20% increase in sum of diameters of target lesions taking as a reference smallest sum recorded since start of treatment or unequivocal progression in non-target lesions or appearance of 1 or more new lesions. Analysis of PFS was based on investigator assessment of disease progression. Subjects who were not known to have had PFS event at analysis date were censored at last tumor assessment date prior to data cutoff or date of new treatment initiation, whichever occurred first. Dx+ population: Subset of ITT population, defined prior to first unblinded analysis as meeting threshold for diagnostic score based on ribonucleic acid sequencing data from tumor tissue. '99999'= data not available as upper limit of 95% CI was not reached due to insufficient number of events. “Number of Subjects Analysed” = subjects evaluable for endpoint.

End point type	Primary

End point timeframe:

From randomization until PD, last tumor assessment without PD before new antitumor treatment initiation or death due to any cause, whichever occurred first (up to the data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	26	15	20
Units: months				
median (confidence interval 95%)	16.5 (11.0 to 99999)	4.3 (1.9 to 10.9)	6.0 (2.3 to 26.7)	5.3 (1.8 to 6.7)

Statistical analyses

Statistical analysis title	Cohort 1 (Experimental versus Placebo)

Statistical analysis description:

Hazard ratio was based on stratified Cox regression model.

Comparison groups	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg v Cohort 1: Placebo + Exemestane 25 mg
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0335
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.442
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.205
upper limit	0.995

Statistical analysis title	Cohort 2 (Experimental versus Placebo)
Statistical analysis description:	
Hazard ratio was based on stratified Cox regression model.	
Comparison groups	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg v Cohort 2: Placebo + Exemestane 25 mg
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1936
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.554
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.225
upper limit	1.363

Secondary: Clinical Benefit Rate-24 (CBR-24)

End point title	Clinical Benefit Rate-24 (CBR-24)

End point description:

CBR-24:Subjects (%) with best response of complete response (CR), partial response (PR) or stable disease (SD) sustained >=24 weeks, determined by investigator using RECIST 1.1. CR:Disappearance of all lesions and normalization of tumor marker level for non-target lesions, also, lymph nodes must be non-pathological in size (less than [<] 10 millimeter [mm] short axis). PR:>=30% decrease in sum of diameters of target lesions, using baseline sum diameters as reference. SD: Neither sufficient reduction to qualify as PR nor sufficient increase to qualify as PD, using the smallest sum diameters as reference. PD:>=20% increase in sum of diameters of target lesions, using smallest sum as reference (including baseline), also, the sum must demonstrate an absolute increase of at least 5 mm, or unequivocal progression of existing non-target lesions or appearance of 1 or more new target or non-target lesions. ITT population included all subjects randomly assigned to double-blind study treatment.

End point type	Secondary

End point timeframe:

From randomization up to the data cutoff date (23 Sep 2016)

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	60	60
Units: percentage of subjects				
number (confidence interval 95%)	61.9 (48.8 to 73.9)	45.3 (38.2 to 58.3)	20.0 (10.8 to 32.3)	31.7 (20.3 to 45.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Best Objective Response Rate (BORR)

End point title	Best Objective Response Rate (BORR)

End point description:

BORR: Subjects (%) with measurable disease and best response of CR or PR using RECIST 1.1. CR:Disappearance of all lesions and normalization of tumor marker level for non-target lesions, also, lymph nodes must be non-pathological in size (<10 mm short axis). PR:>=30% decrease in sum of diameters of target lesions, using baseline sum diameters as reference. SD: Neither sufficient reduction to qualify as PR nor sufficient increase to qualify as PD, using smallest sum diameters as reference. PD:>=20% increase (absolute increase of >=5 mm) in sum of diameters of target lesions, using smallest sum as reference (including baseline), or unequivocal progression of existing non-target lesions, or appearance of 1 or more new lesions. ITT population included all subjects randomly assigned to double-blind study treatment. Here 'Number of subjects analyzed' signifies subjects evaluable for this

End point type	Secondary

End point timeframe:

From randomization until CR or PR, whichever occurred first (up to the data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	42	42	42
Units: percentage of subjects				
number (confidence interval 95%)	30.8 (17.0 to 47.6)	19.0 (8.6 to 34.1)	9.5 (2.7 to 22.6)	4.8 (0.6 to 16.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response (DOR)

End point title	Duration of Objective Response (DOR)

End point description:

DOR: Time from first documentation of CR or PR, to first documentation of PD or death due to any cause, whichever occurred first, using RECIST 1.1. CR: Disappearance of all lesions and normalization of tumor marker level for non-target lesions, also, lymph nodes must be non-pathological in size (<10 mm short axis). PR: >=30% decrease in sum of diameters of target lesions, using baseline sum diameters as reference. SD: Neither sufficient reduction to qualify as PR nor sufficient increase to qualify as PD, using smallest sum diameters as reference. PD: >=20% increase (absolute increase of >=5 mm) in sum of diameters of target lesions, compared to smallest sum, or unequivocal progression of existing non-target lesions, or appearance of 1 or more new lesions. ITT population. 'Number of subjects analyzed' signifies subjects evaluable for this endpoint. '99999' signifies data not available as upper limit of 95% confidence interval was not reached due to insufficient number of events.

End point type	Secondary

End point timeframe:

From first documentation of CR or PR until PD, last tumor assessment without PD before new antitumor treatment initiation or death due to any cause, whichever occurred first (up to the data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	42	42	42
Units: months				
median (confidence interval 95%)	14.0 (5.6 to 99999)	9.1 (3.2 to 10.2)	18.3 (3.3 to 23.1)	4.6 (1.9 to 7.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response: Time from randomization to first documentation of CR or PR. CR: Disappearance of all (target and non-target) lesions and normalization of tumor marker level for non-target lesions. All lymph nodes (target and non-target) must be non-pathological in size (< 10 mm short axis). PR: >=30% decrease in the sum of diameters of target lesions, using baseline sum diameters as a reference. Subjects with no CR or PR were censored at last tumor assessment date prior to data cutoff or date of new treatment initiation, whichever occurred first. ITT population. 'Number of subjects analyzed' signifies subjects evaluable for this endpoint. '99999' signifies data not available as either, median and/ or upper limit of 95% confidence interval, or median and 95% confidence interval were not reached due to insufficient number of events at the time of data cutoff.

End point type	Secondary

End point timeframe:

From randomization until first documentation of CR, PR, last tumor assessment without PD before new antitumor treatment initiation or death due to any cause, whichever occurred first (up to the data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	42	42	42
Units: months				
median (confidence interval 95%)	12.9 (7.3 to 99999)	14.0 (7.4 to 99999)	99999 (3.9 to 99999)	99999 (99999 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time to progression was defined as the time from the date of randomization to PD defined by the investigator using RECIST 1.1. PD: >=20% increase in the sum of diameters of target lesions, using the smallest sum during the study as a reference (including baseline sum if it is the smallest), also, the sum must demonstrate an absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions or appearance of 1 or more new lesions (target or non-target). Subjects who did not experience disease progression, time to progression was right censored at the date of the last tumor assessment prior to data cutoff or date of new antitumor treatment, whichever occurred first. ITT population included all the subjects randomly assigned to double-blind study treatment.

End point type	Secondary

End point timeframe:

From randomization until PD or last tumor assessment without PD before new antitumor treatment initiation, whichever occurred first (up to the data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	60	60
Units: months				
median (confidence interval 95%)	11.8 (7.3 to 15.9)	7.4 (3.5 to 13.5)	3.6 (1.9 to 5.6)	3.9 (2.6 to 5.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) at 6 Months

End point title	Progression Free Survival (PFS) at 6 Months

End point description:

PFS at 6 months was defined as the percentage of subjects with no event of disease progression at Month 6 landmark, estimated by Kaplan-Meier methods. PFS was defined as the time in months from randomization to the first documentation of PD or death on study due to any cause, whichever occurred first. PD: >=20% increase in the sum of diameters of target lesions, using the smallest sum during the study as a reference (including baseline sum if it is the smallest), also, the sum must demonstrate an absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions or appearance of 1 or more new lesions (target or non-target). The analysis of PFS was based on investigator assessment of disease progression. ITT population included all the subjects randomly assigned to double-blind study treatment.

End point type	Secondary

End point timeframe:

Month 6

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	60	60
Units: percentage of subjects				
number (confidence interval 95%)	66.7 (53.2 to 77.0)	50.0 (37.1 to 61.6)	31.5 (19.7 to 43.9)	33.3 (21.6 to 45.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration Versus Time Summary of Enzalutamide

End point title	Concentration Versus Time Summary of Enzalutamide

End point description:

Concentration versus time summary was calculated by setting concentration values below limit of quantitation to zero. Pharmacokinetic (PK) population for enzalutamide included all subjects in safety population who received any amount of enzalutamide and had at least 1 reportable concentration value for enzalutamide or its active metabolite (N-desmethyl enzalutamide). Here, ''n'' signifies number of subjects evaluable at each specified time-point.

End point type	Secondary

End point timeframe:

Predose on Day 29, 57 and 113

End point values	Enzalutamide 160 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	114			
Units: microgram per milliliter				
arithmetic mean (standard deviation)				
Day 29 (n = 109)	14.2 (± 2.97)			
Day 57 (n = 92)	14.2 (± 3.21)			
Day 113 (n = 67)	13.2 (± 4.51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration Versus Time Summary of Exemestane

End point title	Concentration Versus Time Summary of Exemestane

End point description:

Concentration versus time summary was calculated by setting concentration values below limit of quantitation to zero. PK population for exemestane was defined as all subjects in the safety population who received any amount of exemestane and had at least 1 reportable plasma concentration value for exemestane. Here, ‘’n’’ signifies number of subjects evaluable at each specified time-point. Here '99999' signifies data not available as either no subjects were evaluable, or only one subject was evaluable at specified time points.

End point type	Secondary

End point timeframe:

Predose, 1 and 6 hour postdose on Day 29, 57, 113 and 169

End point values	Exemestane 25 mg	Exemestane 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	114	115		
Units: Picogram per milliliter				
arithmetic mean (standard deviation)				
Day 29: Predose (n=108, 108)	1010 (± 1600)	943 (± 939)		
Day 29: 1 hour Postdose (n=99, 102)	17000 (± 16400)	19200 (± 17800)		
Day 29: 6 hour Postdose (n=57, 55)	5590 (± 4750)	6850 (± 9090)		
Day 57: Predose (n=89, 92)	1160 (± 2590)	1100 (± 2650)		
Day 57: 1 hour Postdose (n=76, 83)	19900 (± 18600)	15300 (± 14500)		
Day 57: 6 hour Postdose (n=26, 23)	5890 (± 4880)	5650 (± 6200)		
Day 113: Predose (n=65, 68)	1160 (± 2870)	1330 (± 3380)		
Day 113: 1 hour Postdose (n=58, 58)	20800 (± 18100)	19400 (± 18500)		
Day 113: 6 hour Postdose (n=12, 14)	3510 (± 3850)	5600 (± 5290)		
Day 169: Predose (n=0, 0)	99999 (± 99999)	99999 (± 99999)		
Day 169: 1 hour Postdose (n=0, 1)	99999 (± 99999)	22800 (± 99999)		

Day 169: 6 hour Postdose (n=0, 1)	99999 (± 99999)	6020 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration Versus Time Summary of N-desmethyl Enzalutamide

End point title	Concentration Versus Time Summary of N-desmethyl Enzalutamide

End point description:

N-desmethyl enzalutamide was the active metabolite of enzalutamide. Concentration versus time summary was calculated by setting concentration values below limit of quantitation to zero. PK population for N-desmethyl enzalutamide included all the subjects in safety population who received any amount of enzalutamide and had at least 1 reportable concentration value for N-desmethyl enzalutamide. Here, ''n'' signifies number of subjects evaluable at each specified time-point.

End point type	Secondary

End point timeframe:

Predose on Day 29, 57 and 113

End point values	Enzalutamide 160 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	114			
Units: microgram per milliliter				
arithmetic mean (standard deviation)				
Day 29 (n = 109)	11.6 (± 4.10)			
Day 57 (n = 92)	15.2 (± 4.76)			
Day 113 (n = 67)	15.2 (± 5.81)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Core Questionnaire (QLQ-C30)

End point title	European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Core Questionnaire (QLQ-C30)

End point description:

End point type	Other pre-specified

End point timeframe:

Month 24

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[1]	0[2]	0[3]	0[4]
Units: units on a scale				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[1] - Data was not analyzed at this time point and will be reported at the time of final analysis.

[2] - Data was not analyzed at this time point and will be reported at the time of final analysis.

[3] - Data was not analyzed at this time point and will be reported at the time of final analysis.

[4] - Data was not analyzed at this time point and will be reported at the time of final analysis.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Module (QLQ-BR23)

End point title	European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Module (QLQ-BR23)

End point description:

End point type	Other pre-specified

End point timeframe:

Month 24

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[5]	0[6]	0[7]	0[8]
Units: units on a scale				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[5] - Data was not analyzed at this time point and will be reported at the time of final analysis.

[6] - Data was not analyzed at this time point and will be reported at the time of final analysis.

[7] - Data was not analyzed at this time point and will be reported at the time of final analysis.

[8] - Data was not analyzed at this time point and will be reported at the time of final analysis.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Positive Androgen Receptor (AR) Expression by Immunohistochemistry (IHC)

End point title	Number of Subjects With Positive Androgen Receptor (AR) Expression by Immunohistochemistry (IHC)

End point description:

End point type	Other pre-specified

End point timeframe:

Day 1, 29, 57, 113 and 169

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[9]	0[10]	0[11]	0[12]
Units: subjects				

Notes:

[9] - Protocol was amended and data not analyzed as per planned analysis.

[10] - Protocol was amended and data not analyzed as per planned analysis.

[11] - Protocol was amended and data not analyzed as per planned analysis.

[12] - Protocol was amended and data not analyzed as per planned analysis.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 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)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. 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 was defined as an event that emerged during the treatment period that was absent before treatment, or worsened during the treatment period relative to the pretreatment state. AEs included both serious and non-serious AEs. Safety population included all the subjects who received study drug either in double blind or in open label treatment period.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after the last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first (up to data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	63	60	60
Units: subjects				
AEs	59	58	58	53
SAEs	15	12	10	8

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events of Grade 3 or Higher Severity

End point title	Number of Subjects With Treatment-Emergent Adverse Events of Grade 3 or Higher Severity

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Severity of the AEs was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Only the subjects with treatment-emergent AEs of grade 3 (severe) or higher grade were reported in this endpoint. Safety population included all the subjects who received study drug either in double blind or in open label treatment period.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after the last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first (up to data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	63	60	60
Units: subjects	20	15	22	12

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Clinically Significant Vital Sign Abnormalities

End point title	Number of Subjects With Clinically Significant Vital Sign Abnormalities

End point description:

Clinically significant vital sign abnormality criteria: Systolic blood pressure (SBP): absolute SBP <90 millimeters of mercury (mmHg) and decrease from baseline (DFB) >30 mmHg, absolute SBP>180 mmHg and increase from baseline (IFB) >40 mmHg, final visit or 2 consecutive visits SBP >=20 mmHg change from baseline (CFB), most extreme post-baseline (MEPB) SBP >=140 mmHg, MEPB SBP >=180 mmHg, most extreme SBP >=140 mmHg and >=20 mmHg CFB, most extreme SBP >=180 mmHg and >=20 mmHg CFB; diastolic blood pressure (DBP): absolute DBP >105 mmHg and IFB >30 mmHg, absolute DBP <50 mmHg and DFB >20 mmHg, final visit or 2 consecutive visits DBP >=15 mmHg CFB, MEPB DBP >=90 mmHg, MEPB DBP >=105 mmHg, most extreme DBP >=90 mmHg and >=15 mmHg CFB, most extreme DBP >=105 mmHg and >=15 mmHg CFB; heart rate (HR) <50 beats per minute (BPM) and DFB >20 BPM or HR >120 BPM and IFB >30 BPM. Safety population included all subjects who received study drug in double blind or in open label treatment period.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after the last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first (up to data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	63	60	60
Units: subjects				
Blood pressure	36	39	43	24
Heart rate	0	2	0	0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Clinically Significant Laboratory Abnormalities

End point title	Number of Subjects With Clinically Significant Laboratory Abnormalities

End point description:

Laboratory tests included hematology (hematocrit, hemoglobin, platelet count, red blood cell count, total neutrophils [absolute] and white blood cell count with differential) and serum chemistry (albumin, alkaline phosphatase, alanine aminotransferase [ALT], aspartate transaminase [AST], blood urea nitrogen and creatinine, calcium, sodium, potassium, chloride, glucose (non-fasting), lactate dehydrogenase, magnesium, phosphorus/phosphate, total bilirubin, total bicarbonate, total protein and uric acid). Clinically significant abnormality evaluation was based on clinical investigator’s judgment. Safety population included all the subjects who received study drug either in double blind or in open label treatment period.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 days after the last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first (up to data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	63	60	60
Units: subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression Free Survival (PFS): by Electronic Data Capture (EDC)

End point title	Progression Free Survival (PFS): by Electronic Data Capture (EDC)

End point description:

PFS=time in months from randomization to first (1st) documentation of PD or death on study due to any cause, whichever occurred 1st. PD by RECIST 1.1: >=20% increase in sum of diameters of target lesions (TLs) taking as a reference the smallest sum recorded since start of treatment or unequivocal progression in non-TLs or appearance of 1 or more new lesions. Analysis of PFS was based on investigator assessment of PD. Subjects not known to have had PFS event at analysis date were censored at last tumor assessment date prior to data cutoff or date of new treatment initiation, whichever occurred 1st. Analysis performed on all randomized subjects. Randomization to cohort based on subject's exposure to advance setting hormonal therapy. Initial randomization done by IWRS. Later,upon detailed data entry in EDC, it was determined 1 subject incorrectly assigned to Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg by IWRS, so counted in Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg by EDC.

End point type	Other pre-specified

End point timeframe:

From randomization until PD, last tumor assessment without PD before new antitumor treatment initiation or death due to any cause, whichever occurred first (up to the data cutoff date [23 Sep 2016])

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg (EDC)	Cohort 1: Placebo + Exemestane 25 mg (EDC)	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg (EDC)	Cohort 2: Placebo + Exemestane 25 mg (EDC)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	64	61	60
Units: months				
median (confidence interval 95%)	11.8 (7.3 to 14.6)	5.8 (3.5 to 10.9)	3.6 (1.9 to 5.6)	3.9 (2.6 to 5.4)

Statistical analyses

Statistical analysis title	Cohort 1 (Experimental versus Placebo)

Statistical analysis description:

Hazard ratio was based on stratified Cox regression model.

Comparison groups	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg (EDC) v Cohort 1: Placebo + Exemestane 25 mg (EDC)
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7378
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.928
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.599
upper limit	1.438

Statistical analysis title	Cohort 2 (Experimental versus Placebo)
Statistical analysis description:	
Hazard ratio was based on stratified Cox regression model.	
Comparison groups	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg (EDC) v Cohort 2: Placebo + Exemestane 25 mg (EDC)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8817
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.968
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.632
upper limit	1.483

Other pre-specified: Progression Free Survival (PFS): Diagnostic Positive (DX+) Population By Electronic Data Capture (EDC)

End point title	Progression Free Survival (PFS): Diagnostic Positive (DX+) Population By Electronic Data Capture (EDC)

End point description:

PFS: time in months from randomization to first documentation of PD or death on study due to any cause, whichever occurred first. PD (as per RECIST 1.1): >= 20% increase in sum of diameters of target lesions taking as a reference smallest sum recorded since start of treatment or unequivocal progression in non-target lesions or appearance of 1 or more new lesions. Analysis of PFS was based on investigator assessment of disease progression. Subjects who were not known to have had PFS event at analysis date were censored at last tumor assessment date prior to data cutoff or date of new treatment initiation, whichever occurred first. Dx+ population: Subset of ITT population, defined prior to first unblinded analysis as meeting threshold for diagnostic score based on ribonucleic acid sequencing data from tumor tissue. '99999'= data not available as upper limit of 95% CI was not reached due to insufficient number of events. “Number of Subjects Analysed” = subjects evaluable for endpoint.

End point type	Other pre-specified

End point timeframe:

From randomization until PD, last tumor assessment without PD before new antitumor treatment initiation or death due to any cause, whichever occurred first (up to 3 years)

End point values	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg (EDC)	Cohort 1: Placebo + Exemestane 25 mg (EDC)	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg (EDC)	Cohort 2: Placebo + Exemestane 25 mg (EDC)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	26	16	20
Units: Months				
median (confidence interval 95%)	16.9 (11.0 to 99999)	4.3 (1.9 to 10.9)	6.0 (3.5 to 16.6)	5.3 (1.8 to 6.7)

Statistical analyses

Statistical analysis title	Cohort 1 (Experimental versus Placebo)
Statistical analysis description:	
Hazard ratio was based on stratified Cox regression model.	
Comparison groups	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg (EDC) v Cohort 1: Placebo + Exemestane 25 mg (EDC)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.127
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.522
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.224
upper limit	1.217

Statistical analysis title	Cohort 2 (Experimental versus Placebo)
Statistical analysis description:	
Hazard ratio was based on stratified Cox regression model.	
Comparison groups	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg (EDC) v Cohort 2: Placebo + Exemestane 25 mg (EDC)

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0359
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.143
upper limit	0.961

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after the last dose of study drug or before initiation of a new antitumor treatment, whichever occurred first (up to data cutoff date [23 Sep 2016])

Adverse event reporting additional description:

Same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another subject, or one subject may have experienced both a serious and non-serious event during the study. AEs and SAEs were collected for safety population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg

Reporting group description:

Subjects with no previous hormonal treatment for advanced breast cancer, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Cohort 1: Placebo + Exemestane 25 mg

Reporting group description:

Subjects with no previous hormonal treatment for advanced breast cancer received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg

Reporting group description:

Subjects with previous disease progression following hormonal treatment for advanced breast cancer, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Reporting group title	Cohort 2: Placebo + Exemestane 25 mg

Reporting group description:

Subjects with previous disease progression following hormonal treatment for advanced breast cancer, received placebo matched to enzalutamide along with exemestane 25 mg, orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Eligible subjects with disease progression in double blind period, on their discretion, received enzalutamide 160 mg along with exemestane 50 mg, orally, once daily up to disease progression in open label treatment period. Subjects were followed-up until 30 days after last dose of study drug, death, or before initiation of a new antitumor treatment, whichever occurred first.

Serious adverse events	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 62 (24.19%)	12 / 63 (19.05%)	10 / 60 (16.67%)

number of deaths (all causes)	2	8	3
number of deaths resulting from adverse events	2	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA PANCREAS			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BREAST CANCER			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (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
BREAST CANCER METASTATIC			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (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
CONTRALATERAL BREAST CANCER			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHANGIOSIS CARCINOMATOSA			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (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
MALIGNANT ASCITES			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	2 / 62 (3.23%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
METASTASES TO CENTRAL NERVOUS SYSTEM			

subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTATIC PAIN			
subjects affected / exposed	1 / 62 (1.61%)	1 / 63 (1.59%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLASMA CELL MYELOMA			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (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
CHILLS			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (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
DISEASE PROGRESSION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
FACIAL PAIN			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FATIGUE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			

subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (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
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
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			
DYSPNOEA			
subjects affected / exposed	1 / 62 (1.61%)	1 / 63 (1.59%)	0 / 60 (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 EXERTIONAL			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PLEURAL EFFUSION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (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
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
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			
DELIRIUM			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDAL IDEATION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (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
HUMERUS FRACTURE			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (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
LACERATION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (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
OPTIC NERVE INJURY			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

RADIATION PNEUMONITIS			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRAUMATIC HAEMORRHAGE			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
BRACHIAL PLEXOPATHY			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
DIZZINESS			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (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
EMBOLIC STROKE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

GRAND MAL CONVULSION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
INTRACRANIAL HAEMATOMA			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPEECH DISORDER			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (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
STATUS EPILEPTICUS			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (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	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			

subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
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			
FAECES DISCOLOURED			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL STENOSIS			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (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
VOMITING			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
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			
CHOLECYSTITIS			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC HAEMORRHAGE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

RENAL FAILURE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MASTICATION DISORDER			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECK PAIN			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (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
PATHOLOGICAL FRACTURE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BREAST CELLULITIS			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			

subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPERCALCAEMIA			
subjects affected / exposed	2 / 62 (3.23%)	0 / 63 (0.00%)	2 / 60 (3.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOPHOSPHATAEMIA			

subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	0 / 60 (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

Serious adverse events	Cohort 2: Placebo + Exemestane 25 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 60 (13.33%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA PANCREAS			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BREAST CANCER			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BREAST CANCER METASTATIC			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CONTRALATERAL BREAST CANCER			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LYMPHANGIOSIS CARCINOMATOSA			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MALIGNANT ASCITES			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

MALIGNANT PLEURAL EFFUSION				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
METASTASES TO CENTRAL NERVOUS SYSTEM				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
METASTATIC PAIN				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PLASMA CELL MYELOMA				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
ASTHENIA				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHILLS				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DISEASE PROGRESSION				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FACIAL PAIN				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

FATIGUE				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GENERAL PHYSICAL HEALTH DETERIORATION				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INFLUENZA LIKE ILLNESS				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
NON-CARDIAC CHEST PAIN				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PAIN				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
ANAPHYLACTIC REACTION				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DRUG HYPERSENSITIVITY				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
DYSPNOEA				

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PLEURAL EFFUSION			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
DELIRIUM			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SUICIDAL IDEATION			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HUMERUS FRACTURE			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

LACERATION				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OPTIC NERVE INJURY				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RADIATION PNEUMONITIS				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SPINAL COMPRESSION FRACTURE				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
TRAUMATIC HAEMORRHAGE				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
CARDIAC FAILURE CONGESTIVE				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
BRACHIAL PLEXOPATHY				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CEREBROVASCULAR ACCIDENT				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

DIZZINESS				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
EMBOLIC STROKE				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GRAND MAL CONVULSION				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HAEMORRHAGE INTRACRANIAL				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INTRACRANIAL HAEMATOMA				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SPEECH DISORDER				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SPINAL CORD COMPRESSION				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
STATUS EPILEPTICUS				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SYNCOPE				

subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
FAECES DISCOLOURED			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
OESOPHAGEAL STENOSIS			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
VOMITING			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

CHOLECYSTITIS				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HEPATIC HAEMORRHAGE				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
RENAL FAILURE				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
BACK PAIN				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MASTICATION DISORDER				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
NECK PAIN				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PAIN IN EXTREMITY				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PATHOLOGICAL FRACTURE				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
BREAST CELLULITIS			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PYELONEPHRITIS			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
WOUND INFECTION			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
HYPERCALCAEMIA			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
HYPONATRAEMIA			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 1: Placebo + Exemestane 25 mg	Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 62 (95.16%)	58 / 63 (92.06%)	58 / 60 (96.67%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	3
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 62 (0.00%)	4 / 63 (6.35%)	2 / 60 (3.33%)
occurrences (all)	0	4	3
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	19 / 62 (30.65%)	14 / 63 (22.22%)	14 / 60 (23.33%)
occurrences (all)	21	16	19
HYPERTENSION			

subjects affected / exposed	6 / 62 (9.68%)	4 / 63 (6.35%)	0 / 60 (0.00%)
occurrences (all)	7	4	0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	8 / 62 (12.90%)	4 / 63 (6.35%)	5 / 60 (8.33%)
occurrences (all)	8	4	5
HEADACHE			
subjects affected / exposed	9 / 62 (14.52%)	6 / 63 (9.52%)	9 / 60 (15.00%)
occurrences (all)	10	6	12
AMNESIA			
subjects affected / exposed	4 / 62 (6.45%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences (all)	4	0	0
COGNITIVE DISORDER			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
DISTURBANCE IN ATTENTION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	4
NEUROPATHY PERIPHERAL			
subjects affected / exposed	4 / 62 (6.45%)	3 / 63 (4.76%)	0 / 60 (0.00%)
occurrences (all)	4	3	0
PARAESTHESIA			
subjects affected / exposed	4 / 62 (6.45%)	2 / 63 (3.17%)	0 / 60 (0.00%)
occurrences (all)	5	2	0
SOMNOLENCE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 62 (6.45%)	1 / 63 (1.59%)	6 / 60 (10.00%)
occurrences (all)	11	1	8
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	10 / 62 (16.13%)	7 / 63 (11.11%)	6 / 60 (10.00%)
occurrences (all)	9	7	8
FATIGUE			

subjects affected / exposed	23 / 62 (37.10%)	21 / 63 (33.33%)	22 / 60 (36.67%)
occurrences (all)	29	24	24
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
PAIN			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
PYREXIA			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	10 / 62 (16.13%)	7 / 63 (11.11%)	8 / 60 (13.33%)
occurrences (all)	10	7	10
DIARRHOEA			
subjects affected / exposed	12 / 62 (19.35%)	10 / 63 (15.87%)	6 / 60 (10.00%)
occurrences (all)	16	10	8
DYSPEPSIA			
subjects affected / exposed	1 / 62 (1.61%)	6 / 63 (9.52%)	5 / 60 (8.33%)
occurrences (all)	1	6	5
NAUSEA			
subjects affected / exposed	24 / 62 (38.71%)	10 / 63 (15.87%)	18 / 60 (30.00%)
occurrences (all)	33	11	23
VOMITING			
subjects affected / exposed	11 / 62 (17.74%)	7 / 63 (11.11%)	6 / 60 (10.00%)
occurrences (all)	17	12	8
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	4
ABDOMINAL PAIN			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			

COUGH			
subjects affected / exposed	9 / 62 (14.52%)	6 / 63 (9.52%)	2 / 60 (3.33%)
occurrences (all)	10	7	2
DYSPNOEA			
subjects affected / exposed	9 / 62 (14.52%)	7 / 63 (11.11%)	5 / 60 (8.33%)
occurrences (all)	10	8	7
OROPHARYNGEAL PAIN			
subjects affected / exposed	4 / 62 (6.45%)	2 / 63 (3.17%)	0 / 60 (0.00%)
occurrences (all)	4	2	0
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	8 / 62 (12.90%)	3 / 63 (4.76%)	5 / 60 (8.33%)
occurrences (all)	9	3	5
RASH			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	4
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	7 / 62 (11.29%)	4 / 63 (6.35%)	0 / 60 (0.00%)
occurrences (all)	8	4	0
INSOMNIA			
subjects affected / exposed	5 / 62 (8.06%)	4 / 63 (6.35%)	5 / 60 (8.33%)
occurrences (all)	5	4	5
DEPRESSED MOOD			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	4
DEPRESSION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	14 / 62 (22.58%)	11 / 63 (17.46%)	10 / 60 (16.67%)
occurrences (all)	16	14	11
BACK PAIN			
subjects affected / exposed	11 / 62 (17.74%)	5 / 63 (7.94%)	4 / 60 (6.67%)
occurrences (all)	11	6	5

BONE PAIN			
subjects affected / exposed	2 / 62 (3.23%)	4 / 63 (6.35%)	5 / 60 (8.33%)
occurrences (all)	2	4	6
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	7 / 62 (11.29%)	4 / 63 (6.35%)	2 / 60 (3.33%)
occurrences (all)	9	4	3
MUSCULOSKELETAL PAIN			
subjects affected / exposed	7 / 62 (11.29%)	1 / 63 (1.59%)	0 / 60 (0.00%)
occurrences (all)	8	2	0
MYALGIA			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	8 / 62 (12.90%)	8 / 63 (12.70%)	3 / 60 (5.00%)
occurrences (all)	6	13	5
MUSCULOSKELETAL STIFFNESS			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Infections and infestations			
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	2 / 62 (3.23%)	4 / 63 (6.35%)	0 / 60 (0.00%)
occurrences (all)	2	5	0
Nasopharyngitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 63 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	6 / 62 (9.68%)	6 / 63 (9.52%)	6 / 60 (10.00%)
occurrences (all)	9	6	7

Non-serious adverse events	Cohort 2: Placebo + Exemestane 25 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 60 (88.33%)		

Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	9 / 60 (15.00%)		
occurrences (all)	10		
HYPERTENSION			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
HEADACHE			
subjects affected / exposed	10 / 60 (16.67%)		
occurrences (all)	17		
AMNESIA			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
COGNITIVE DISORDER			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
DISTURBANCE IN ATTENTION			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
NEUROPATHY PERIPHERAL			

subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
PARAESTHESIA			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
SOMNOLENCE			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	9		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	8		
FATIGUE			
subjects affected / exposed	13 / 60 (21.67%)		
occurrences (all)	16		
OEDEMA PERIPHERAL			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
PAIN			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
PYREXIA			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	8 / 60 (13.33%)		
occurrences (all)	9		
DIARRHOEA			
subjects affected / exposed	10 / 60 (16.67%)		
occurrences (all)	15		
DYSPEPSIA			

subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all) ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) ABDOMINAL PAIN subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4 11 / 60 (18.33%) 17 3 / 60 (5.00%) 4 2 / 60 (3.33%) 3 4 / 60 (6.67%) 5		
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) DYSPNOEA subjects affected / exposed occurrences (all) OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 5 5 / 60 (8.33%) 5 0 / 60 (0.00%) 0		
Skin and subcutaneous tissue disorders ALOPECIA subjects affected / exposed occurrences (all) RASH subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2 0 / 60 (0.00%) 0		
Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all) INSOMNIA	0 / 60 (0.00%) 0		

subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
DEPRESSED MOOD			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
DEPRESSION			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	9		
BACK PAIN			
subjects affected / exposed	12 / 60 (20.00%)		
occurrences (all)	13		
BONE PAIN			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	4		
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
MYALGIA			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	6		
PAIN IN EXTREMITY			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	6		
MUSCULOSKELETAL STIFFNESS			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	2		
Infections and infestations			

URINARY TRACT INFECTION subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 9 0 / 60 (0.00%) 0 1 / 60 (1.67%) 1		
Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2016	To add an open-label period if the study met its primary endpoint.
01 February 2017	To define and analyze subject cohorts by gene expression status rather than Immunohistochemistry analysis of breast tumor tissue for nuclear androgen receptor staining.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported