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	23 August 2024

Results information

Result version number	v4 (current)
This version publication date	05 September 2025
First version publication date	14 October 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	C3431008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02007512
WHO universal trial number (UTN)	-
Other trial identifiers	Other study ID: MDV3100-12

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	66 Hudson Boulevard East, New York, United States, NY 10001-2192
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	Final
Date of interim/final analysis	13 January 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 August 2024
Was the trial ended prematurely?	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 participants with advanced breast cancer.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 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	109

Notes:

Subjects enrolled per age group

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

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

Subject disposition

Recruitment

Recruitment details:

A total of 247 participants were enrolled.

Pre-assignment

Screening details:

This was a Phase 2, randomized, double blind, placebo-controlled study.

Period 1

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

Blinding implementation details:

Subject and investigator were blinded.

Arms

Are arms mutually exclusive?	No
Arm title	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg

Arm description:

Participants 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. Participants 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	MDV3100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Enzalutamide 160 mg was received once daily as 4 capsules (40 mg each).

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 received orally.

Arm title	Double blind Cohort 1: Placebo + Exemestane 25 mg

Arm description:

Participants 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 participants 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. Participants 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 capsule matched to enzalutamide was received 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 received orally, once daily.

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

Arm description:

Participants 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. Participants 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	MDV3100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Enzalutamide 160 mg was received once daily as 4 capsules (40 mg each).

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 received orally.

Arm title	Double blind Cohort 2: Placebo + Exemestane 25 mg

Arm description:

Participants 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 participants 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. Participants 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 capsule matched to enzalutamide was received 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 received orally, once daily.

Arm title	Open label Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg

Arm description:

Participants 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 participants 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. Participants 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	MDV3100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Enzalutamide 160 mg was received once daily as 4 capsules (40 mg each).

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 received orally.

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

Arm description:

Participants 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 participants 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. Participants 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 received orally.

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 received once daily as 4 capsules (40 mg each).

Number of subjects in period 1	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg
Started	63	64	60
Treated	62	63	60
Completed	0	0	0
Not completed	63	64	60
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	3	3	3
Disease progression	51	57	50
Adverse event, non-fatal	4	2	6
Randomised but not treated	1	1	-
Unspecified	2	1	1
Protocol deviation	1	-	-

Number of subjects in period 1	Double blind Cohort 2: Placebo + Exemestane 25 mg	Open label Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Open label Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg
Started	60	25	12
Treated	60	24	11
Completed	0	0	0
Not completed	60	25	12
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	3	-	-
Disease progression	52	23	11
Adverse event, non-fatal	2	1	-
Randomised but not treated	-	-	-
Unspecified	2	1	1
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups

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

Reporting group description:

Participants 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. Participants 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	Double blind Cohort 1: Placebo + Exemestane 25 mg

Reporting group description:

Participants 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 participants 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. Participants 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	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg

Reporting group description:

Participants 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. Participants 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	Double blind Cohort 2: Placebo + Exemestane 25 mg

Reporting group description:

Participants 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 participants 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. Participants 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	Open label Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg

Reporting group description:

Participants 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 participants 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. Participants 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	Open label Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg

Reporting group description:

Participants 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 participants 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. Participants 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	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg
Number of subjects	63	64	60
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	42	32	37
>=65 years	21	32	23
Age continuous Units: years			
arithmetic mean	59.0	63.5	60.1
standard deviation	± 10.82	± 11.56	± 11.27
Gender categorical Units: Subjects			
Male	0	0	0
Female	63	64	60

Reporting group values	Double blind Cohort 2: Placebo + Exemestane 25 mg	Open label Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Open label Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg
Number of subjects	60	25	12
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	40	12	9
>=65 years	20	13	3
Age continuous Units: years			
arithmetic mean	60.6	63.5	61.8
standard deviation	± 13.47	± 10.22	± 11.68
Gender categorical Units: Subjects			
Male	0	0	0
Female	60	25	12

Reporting group values	Total		
Number of subjects	284		
Age Categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	172		
>=65 years	112		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Male	0		
Female	284		

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

Subject analysis set description:

Participants 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. Participants 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:

Participants received exemestane 25 mg dose orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Participants 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:

Participants 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. Participants 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.

Reporting group values	Enzalutamide 160 mg	Exemestane 25 mg	Exemestane 50 mg
Number of subjects	114	114	115
Age Categorical Units: Subjects			
<=18 years			
Between 18 and 65 years			
>=65 years			
Age continuous Units: years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender categorical Units: Subjects			
Male	0	0	0
Female	0	0	0

End points

End points reporting groups

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

Reporting group description:

Participants 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. Participants 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	Double blind Cohort 1: Placebo + Exemestane 25 mg

Reporting group description:

Participants 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 participants 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. Participants 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	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg

Reporting group description:

Participants 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. Participants 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	Double blind Cohort 2: Placebo + Exemestane 25 mg

Reporting group description:

Participants 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 participants 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. Participants 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	Open label Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg

Reporting group description:

Participants 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 participants 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. Participants 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	Open label Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg

Reporting group description:

Participants 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 participants 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. Participants 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:

Participants 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. Participants 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:

Participants received exemestane 25 mg dose orally, once daily in double blind treatment period until disease progression or permanent treatment discontinuation. Participants 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:

Participants 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. Participants 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.

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

End point title	Progression Free Survival (PFS): Intent-to-Treat (ITT) Population Stratified Analyses By Interactive Web Recognition System (IWRS)[1]

End point description:

PFS was defined as the time in months from randomisation 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. Participants 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. ITT population included all the participants randomly assigned to double-blind study treatment.

End point type	Primary

End point timeframe:

From randomisation 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)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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	Progression Free Survival: ITT Population By IWRS

Statistical analysis description:

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

Comparison groups	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg v Double blind Cohort 2: Placebo + Exemestane 25 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other[2]
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

Notes:

[2] - Hazard ratio was based on stratified Cox regression model.

Statistical analysis title	PFS: Intent-to-Treat Population By IWRS

Statistical analysis description:

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

Comparison groups	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg v Double blind Cohort 1: Placebo + Exemestane 25 mg
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	other[3]
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

Notes:

[3] - Hazard ratio was based on stratified Cox regression model.

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

End point title	Progression Free Survival (PFS): Diagnostic Positive (DX+) Population Stratified Analyses By Interactive Web Recognition System (IWRS)[4]

End point description:

PFS: time from randomisation to first documentation of PD or death on study due to any cause, whichever occurred first. PD per RECIST 1.1: >= 20% increase in sum of diameters of target lesions taking as 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. Participants 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 (RNA) sequencing data from tumor tissue. "Subjects Analyzed"= participants evaluable for this endpoint.99999 =Upper limit (UL)of 95% CI not reached due to insufficient number of participants with events.

End point type	Primary

End point timeframe:

From randomisation 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)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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	Diagnostic Positive Population By IWRS
Comparison groups	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg v Double blind Cohort 2: Placebo + Exemestane 25 mg
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[5]
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

Notes:

[5] - Hazard ratio was based on stratified Cox regression model.

Statistical analysis title	Diagnostic Positive Population By IWRS
Comparison groups	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg v Double blind Cohort 1: Placebo + Exemestane 25 mg

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other[6]
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	0.955

Notes:

[6] - Hazard ratio was based on stratified Cox regression model.

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

End point title	Clinical Benefit Rate-24 (CBR-24)[7]

End point description:

CBR-24: Percentage of participants with best response of complete response (CR), partial response (PR), or stable disease (SD) sustained for at least 24 weeks, determined by investigator using RECIST 1.1. CR: Disappearance of all (target, non-target) lesions, normalization of non-target lesion's tumor marker level. Non-pathological size (< 10-millimeter [mm] short axis) lymph nodes (target, non-target [NT]) included. PR:>=30% decreased target lesion diameter's sum, by baseline sum diameters as reference. SD: Insufficient reduction to qualify as PR, insufficient increase to qualify as PD, by smallest sum diameters during study as reference.PD:>=20% increase (absolute increase of >=5 mm) in sum of target lesion's diameters, by smallest sum during study as reference (including baseline sum),or unequivocal progression of existing NT lesions, or appearance of at least 1 new target or NT lesions. ITT population included all participants randomly assigned to double-blind study treatment.

End point type	Secondary

End point timeframe:

From randomisation up to 3 years

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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 participants				
number (confidence interval 95%)	61.9 (48.8 to 73.9)	45.3 (32.8 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: Time to Response

End point title	Time to Response[8]

End point description:

Time to response: Time from randomisation to first documentation of CR/PR. CR:Disappearance of all(target and NT)lesions, normalized tumor marker level for NT lesions. All lymph nodes must be non-pathological in size.PR:>=30% decreased target lesion's sum of diameters, with baseline sum of diameters as reference.PD:>=20% increased (>=5mm)target lesion's sum of diameters,with smallest sum as reference,or progression of existing non-target lesions,or appearance of atleast 1 new target or NT lesions.Participants not known to have had CR/PR were censored at last tumor assessment date prior to data cutoff or date of new treatment initiation,whichever occurred first.ITT population used."Subjects analyzed"=participants evaluable for endpoint.99999=UL of 95% CI not reached due to insufficient events during data cutoff.88888=Median and UL of 95% CI not reached due to insufficient events during data cutoff.77777=Median and 95% CI not reached due to insufficient events during data cutoff.

End point type	Secondary

End point timeframe:

From randomisation until first documentation of CR or PR, or last tumor assessment without PD or death prior to new antitumor treatment initiation, whichever occurred first (up to 3 years)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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)	88888 (3.9 to 88888)	77777 (77777 to 77777)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response (DOR)

End point title	Duration of Objective Response (DOR)[9]

End point description:

DOR: Time from first documentation of CR/PR to first documentation of PD/death by any cause, whichever occurred first,determined using RECIST 1.1.CR: Disappearance of all (target and NT)lesions, normalisation of tumor marker level for NT lesions. All lymph nodes must be non-pathological in size. PR: >=30% decrease in sum of diameters of target lesions, by baseline sum diameters as reference. PD: >=20% increase (absolute increase of >=5mm) in target lesions sum of diameters, with smallest sum as reference (including baseline sum), or unequivocal progression of existing non-target lesions, or appearance of atleast 1 new target or NT lesions. Participants with no PD or death (after initial CR or PR) at analysis date were censored at last tumor assessment date prior to date of new antitumor treatment or data cutoff. ITT population used."Subjects analyzed"=participants evaluable for this endpoint.99999=UL of 95% CI not reached due to insufficient number of events during data cutoff.

End point type	Secondary

End point timeframe:

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

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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: Best Objective Response Rate

End point title	Best Objective Response Rate[10]

End point description:

Best objective response rate: Percentage of participants with measurable disease and with a best response of CR or PR according to RECIST 1.1. CR: Disappearance of all (target and non-target) lesions and normalisation 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: Atleast 30% decrease in sum of diameters of target lesions, using baseline sum diameters as reference. Response evaluation was based on investigators' judgment. ITT population included all the participants randomly assigned to double-blind study treatment. Here "subjects analysed" signifies participants with measurable response.

End point type	Secondary

End point timeframe:

From randomisation until CR or PR, whichever occurred first (up to 3 years)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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 participants				
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: Progression Free Survival (PFS) at 6 Months

End point title	Progression Free Survival (PFS) at 6 Months[11]

End point description:

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

End point type	Secondary

End point timeframe:

Month 6

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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 participants				
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 participants 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, "Subjects Analysed" signifies subjects evaluable for this endpoint and "n" signifies participants evaluable for the specified rows.

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: Time to Progression

End point title	Time to Progression[12]

End point description:

Time to progression was defined as the time from the date of randomisation to PD defined by the investigator using RECIST 1.1. PD: >=20% increase (an absolute increase of >=5 mm) in sum of diameters of target lesions, using the smallest sum during the study as a reference (including baseline sum), or unequivocal progression of existing nontarget lesions, or appearance of at least 1 new target or non-target lesions. Participants 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 participants randomly assigned to double-blind study treatment.

End point type	Secondary

End point timeframe:

From randomisation until PD or last tumor assessment without PD before new antitumor treatment initiation, whichever occurred first (up to 3 years)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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: 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 participants in the safety population who received any amount of exemestane and had at least 1 reportable plasma concentration value for exemestane. 99999= Standard deviation could not be estimated since only 1 participant was analysed. 88888= Arithmetic mean and standard deviation could not be estimated since 0 participants were analysed. Here, "n" signifies participants evaluable for the specified rows.

End point type	Secondary

End point timeframe:

Predose, 1 and 6 hour post dose 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)	88888 (± 88888)	88888 (± 88888)		
Day 169: 1 hour Postdose (n=0, 1)	88888 (± 88888)	22800 (± 99999)		
Day 169: 6 hour Postdose (n=0, 1)	88888 (± 88888)	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 participants in safety population who received any amount of enzalutamide and had at least 1 reportable concentration value for N-desmethyl enzalutamide. Here, "n" signifies participants evaluable for the specified rows.

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: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Core Questionnaire (QLQ-C30) at Weeks 5, 9, 17, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121 and 133: Global Health/Quality of Life

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Core Questionnaire (QLQ-C30) at Weeks 5, 9, 17, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121 and 133: Global Health/Quality of Life[13]

End point description:

EORTC QLQ-C30 questionnaire: standardized instrument to assess quality of life of cancer participants. Participants self-rated their self-care, activity level, pain/discomfort, and mental health during the past week by choosing 1 of 4 possible responses that recorded level of intensity (not at all, a little, quite a bit, and very much) within each dimension, where higher score=more level of intensity. Questionnaire also asked participants to rate their overall health or quality of life within past week on scale of 1: very poor to 7: excellent. Higher global health/quality scores of life indicated better overall health or quality of life. ITT population evaluated. Here, “Subjects Analyzed” contributed data to table but may not have evaluable data for every row and "n"=participants evaluable for specified rows. 88888=standard deviation (SD) not estimated as 1 participant analysed.99999=arithmetic mean and SD not estimated as 0 participants were analysed.

End point type	Other pre-specified

End point timeframe:

Baseline; Weeks 5, 9, 17, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121 and 133

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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: Units on a scale				
arithmetic mean (standard deviation)				
Week 5 (n=55, 56, 53, 55)	1.2 (± 19.14)	1.3 (± 21.19)	-4.6 (± 16.55)	0.3 (± 15.87)
Week 9 (n=54, 50, 43, 44)	-1.9 (± 21.21)	1.3 (± 18.77)	-5.6 (± 19.13)	-1.3 (± 14.37)
Week 17 (n=42, 38, 25, 30)	-3.0 (± 19.46)	-1.8 (± 19.29)	-7.3 (± 24.45)	-0.8 (± 15.98)
Week 25 (n=37, 34, 15, 21)	3.6 (± 18.17)	-3.4 (± 21.03)	0.6 (± 18.76)	-4.8 (± 16.79)
Week 33 (n=34, 29, 9, 15)	2.2 (± 19.60)	-0.9 (± 19.59)	-8.3 (± 17.68)	-5.0 (± 15.04)
Week 41 (n=29, 22, 9, 12)	-0.9 (± 16.11)	-1.5 (± 16.99)	-9.3 (± 17.40)	-1.4 (± 9.95)
Week 49 (n=25, 21, 7, 8)	-0.7 (± 19.53)	0.8 (± 13.67)	-8.3 (± 12.73)	-4.2 (± 16.06)
Week 61 (n=22, 19, 7, 4)	3.8 (± 18.32)	-5.7 (± 19.26)	-1.2 (± 20.65)	6.3 (± 18.48)
Week 73 (n=15, 13, 7, 4)	-1.1 (± 19.64)	0.0 (± 14.03)	-6.0 (± 15.00)	2.1 (± 21.92)
Week 85 (n=9, 8, 5, 1)	0.9 (± 27.78)	-5.2 (± 7.63)	-3.3 (± 18.26)	0.0 (± 88888)
Week 97 (n=4, 6, 2, 0)	-8.3 (± 6.80)	-2.8 (± 6.80)	0.0 (± 0.00)	99999 (± 99999)
Week 109 (n=3, 1, 2, 0)	-13.9 (± 17.35)	0.0 (± 88888)	12.5 (± 5.89)	99999 (± 99999)
Week 121 (n=0, 1, 0, 0)	99999 (± 99999)	-8.3 (± 88888)	99999 (± 99999)	99999 (± 99999)
Week 133 (n=0, 1, 0, 0)	99999 (± 99999)	0.0 (± 88888)	99999 (± 99999)	99999 (± 99999)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Module (QLQ-BR23) at Weeks 5, 9, 17, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121 and 133

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Module (QLQ-BR23) at Weeks 5, 9, 17, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121 and 133[14]

End point description:

EORTC QLQ-BR23=disease-specific module for breast cancer developed as supplement for EORTC QLQ-C30 that assessed quality of life of breast cancer participants. Participants self-rated on frequent symptoms or problems reported, e.g., pain/discomfort, body satisfaction, self-esteem during past week by choosing 1 of 4 possible responses that recorded level of intensity (not at all, a little, quite a bit, very much) within each dimension. They also self-rated on sexual health/interest during last 4 weeks using same scale. In this endpoint body image functioning, sexual functioning, systemic therapy side effects (SE), upset by hair loss were assessed.ITT population used.Here,"Subjects Analyzed"contributed data to table but may not have evaluable data for every row and "n"=participants evaluable for specified rows. 99999=standard deviation could not be estimated as 1 participant was analysed.88888=arithmetic mean and standard deviation could not be estimated as 0 participants were analysed.

End point type	Other pre-specified

End point timeframe:

Baseline; Weeks 5, 9, 17, 25, 33, 41, 49, 61, 73, 85, 97, 109, 121 and 133

Notes:

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

Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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: Units on a scale				
arithmetic mean (standard deviation)				
Body Image Functioning: Week 5(n=55,57,52,54)	1.8 (± 16.01)	1.9 (± 19.10)	-6.1 (± 13.92)	2.2 (± 15.74)
Body Image Functioning: Week 9(n=53,50,40,44)	-3.5 (± 12.91)	-0.2 (± 17.91)	-3.7 (± 12.51)	2.1 (± 15.58)
Body Image Functioning: Week 17(n=43,38,24,31)	-2.9 (± 20.16)	-3.5 (± 19.24)	-9.0 (± 19.34)	1.3 (± 13.98)
Body Image Functioning: Week 25(n=36,33,15,21)	2.8 (± 16.55)	-7.4 (± 24.24)	-9.4 (± 16.33)	-0.8 (± 7.86)
Body Image Functioning: Week 33(n=34,29,9,14)	-2.9 (± 22.08)	-5.7 (± 17.55)	-1.9 (± 9.11)	-1.8 (± 8.12)
Body Image Functioning: Week 41(n=29,22,9,12)	-2.5 (± 18.76)	-1.3 (± 13.36)	0.0 (± 4.17)	4.2 (± 14.43)
Body Image Functioning: Week 49(n=27,21,7,8)	-2.4 (± 19.79)	-5.2 (± 17.57)	-1.2 (± 3.15)	1.0 (± 8.26)
Body Image Functioning: Week 61(n=20,19,7,4)	3.3 (± 19.94)	-5.7 (± 15.23)	-4.8 (± 6.56)	0.0 (± 13.61)
Body Image Functioning: Week 73(n=14,13,7,4)	-3.2 (± 29.70)	-3.2 (± 12.05)	1.2 (± 5.75)	4.2 (± 10.76)
Body Image Functioning: Week 85(n=10,8,5,1)	8.3 (± 28.05)	-13.5 (± 24.78)	1.7 (± 3.73)	-16.7 (± 99999)
Body Image Functioning: Week 97(n=3,6,2,0)	-5.6 (± 17.35)	-1.4 (± 3.40)	-4.2 (± 5.89)	88888 (± 88888)
Body Image Functioning: Week 109(n=4,1,2,0)	0.0 (± 35.36)	0.0 (± 99999)	-8.3 (± 11.79)	88888 (± 88888)
Body Image Functioning: Week 121(n=0,1,0,0)	88888 (± 88888)	0.0 (± 99999)	88888 (± 88888)	88888 (± 88888)
Body Image Functioning: Week 133(n=0,1,0,0)	88888 (± 88888)	0.0 (± 99999)	88888 (± 88888)	88888 (± 88888)
Sexual Functioning: Week 5(n=53, 52, 50, 53)	1.9 (± 12.08)	-0.3 (± 13.40)	0.3 (± 17.00)	1.9 (± 10.16)
Sexual Functioning: Week 9(n=50, 48, 38, 41)	2.3 (± 16.15)	-1.4 (± 16.78)	1.3 (± 15.68)	2.8 (± 11.73)
Sexual Functioning: Week 17(n=40, 35, 23, 29)	3.3 (± 15.65)	0.0 (± 20.21)	7.2 (± 23.48)	0.6 (± 12.18)
Sexual Functioning: Week 25(n=35, 32, 15, 19)	1.4 (± 17.33)	0.5 (± 19.16)	0.0 (± 25.20)	1.8 (± 10.96)
Sexual Functioning: Week 33(n=33, 28, 9, 12)	4.0 (± 20.43)	3.0 (± 12.05)	7.4 (± 22.22)	4.2 (± 12.56)
Sexual Functioning: Week 41(n=28, 21, 9, 10)	2.4 (± 23.00)	0.8 (± 15.34)	9.3 (± 22.22)	1.7 (± 9.46)
Sexual Functioning: Week 49(n=26, 20, 7, 8)	7.1 (± 21.69)	5.8 (± 11.18)	9.5 (± 26.97)	0.0 (± 0.0)
Sexual Functioning: Week 61(n=18, 18, 7, 4)	7.4 (± 21.56)	1.9 (± 20.52)	7.1 (± 25.20)	0.0 (± 13.61)

Sexual Functioning: Week 73(n=14, 12, 7, 4)	8.3 (± 16.98)	2.8 (± 13.91)	9.5 (± 31.71)	4.2 (± 8.33)
Sexual Functioning: Week 85(n=9, 7, 5, 1)	7.4 (± 22.22)	4.8 (± 15.85)	-6.7 (± 27.89)	0.0 (± 99999)
Sexual Functioning: Week 97(n=3, 5, 2, 0)	-5.6 (± 25.46)	6.7 (± 9.13)	16.7 (± 23.57)	88888 (± 88888)
Sexual Functioning: Week 109(n=3, 1, 2, 0)	0.0 (± 16.67)	0.0 (± 99999)	33.3 (± 0.00)	88888 (± 88888)
Sexual Functioning: Week 121(n=0, 1, 0, 0)	88888 (± 88888)	0.0 (± 99999)	88888 (± 88888)	88888 (± 88888)
Sexual Functioning: Week 133(n=0, 1, 0, 0)	88888 (± 88888)	0.0 (± 99999)	88888 (± 88888)	88888 (± 88888)
Systemic Therapy SE: Week 5(n=55, 57, 54, 54)	4.5 (± 10.59)	3.7 (± 10.06)	7.1 (± 11.49)	3.3 (± 10.82)
Systemic Therapy SE: Week 9(n=53, 51, 42, 45)	7.5 (± 15.24)	2.7 (± 10.24)	6.5 (± 11.32)	3.9 (± 10.77)
Systemic Therapy SE: Week 17(n=43, 38, 25, 31)	7.5 (± 10.81)	2.0 (± 8.79)	7.6 (± 16.61)	6.0 (± 12.51)
Systemic Therapy SE: Week 25(n=37, 34, 15, 21)	8.3 (± 13.90)	2.3 (± 7.35)	5.6 (± 10.86)	5.7 (± 16.05)
Systemic Therapy SE: Week 33(n=35, 29, 9, 14)	6.5 (± 13.54)	-0.2 (± 9.74)	8.5 (± 7.05)	5.3 (± 13.10)
Systemic Therapy SE: Week 41(n=30, 22, 9, 12)	8.4 (± 10.03)	1.3 (± 9.20)	10.6 (± 4.63)	2.0 (± 10.04)
Systemic Therapy SE: Week 49(n=27, 21, 7, 8)	7.8 (± 10.18)	2.5 (± 11.03)	9.7 (± 12.78)	7.7 (± 9.84)
Systemic Therapy SE: Week 61(n=20, 19, 7, 4)	7.6 (± 11.07)	2.5 (± 10.45)	14.7 (± 10.11)	4.8 (± 6.73)
Systemic Therapy SE: Week 73(n=14, 13, 7, 4)	4.9 (± 11.90)	4.4 (± 6.29)	11.6 (± 10.95)	-1.2 (± 5.99)
Systemic Therapy SE: Week 85(n=10, 8, 5, 1)	10.7 (± 12.58)	2.4 (± 8.82)	9.5 (± 6.73)	4.8 (± 99999)
Systemic Therapy SE: Week 97(n=3, 6, 2, 0)	8.2 (± 13.52)	3.2 (± 10.29)	7.1 (± 10.10)	88888 (± 88888)
Systemic Therapy SE: Week 109(n=4, 1, 2, 0)	14.1 (± 9.71)	4.8 (± 99999)	9.5 (± 6.73)	88888 (± 88888)
Systemic Therapy SE: Week 121(n=0, 1, 0, 0)	88888 (± 88888)	9.5 (± 99999)	88888 (± 88888)	88888 (± 88888)
Systemic Therapy SE: Week 133(n=0, 1, 0, 0)	88888 (± 88888)	4.8 (± 99999)	88888 (± 88888)	88888 (± 88888)
Upset by Hair Loss: Week 5(n=12, 11, 18, 12)	-5.6 (± 19.25)	18.2 (± 31.14)	0.0 (± 28.01)	0.0 (± 24.62)
Upset by Hair Loss: Week 9(n=6, 10, 15, 10)	0.0 (± 36.51)	23.3 (± 31.62)	-6.7 (± 18.69)	3.3 (± 24.60)
Upset by Hair Loss: Week 17(n=6, 7, 9, 6)	0.0 (± 21.08)	9.5 (± 16.27)	3.7 (± 20.03)	0.0 (± 36.51)
Upset by Hair Loss: Week 25(n=5, 7, 5, 4)	-6.7 (± 14.91)	28.6 (± 35.63)	26.7 (± 27.89)	-8.3 (± 16.67)
Upset by Hair Loss: Week 33(n=5, 5, 5, 2)	0.0 (± 23.57)	-6.7 (± 14.91)	20.0 (± 29.81)	0.0 (± 0.00)
Upset by Hair Loss: Week 41(n=4, 3, 5, 2)	-16.7 (± 33.33)	0.00 (± 0.00)	13.3 (± 18.26)	16.7 (± 23.57)
Upset by Hair Loss: Week 49(n=5, 2, 3, 2)	6.7 (± 36.51)	0.00 (± 0.00)	11.1 (± 19.25)	0.00 (± 0.00)
Upset by Hair Loss: Week 61(n=3, 2, 4, 0)	11.1 (± 19.25)	16.7 (± 23.57)	25.0 (± 31.91)	88888 (± 88888)
Upset by Hair Loss: Week 73(n=2, 1, 5, 0)	0.0 (± 0.0)	0.0 (± 99999)	40.0 (± 43.46)	88888 (± 88888)
Upset by Hair Loss: Week 85(n=1, 0, 3, 0)	33.3 (± 99999)	88888 (± 88888)	0.0 (± 0.0)	88888 (± 88888)
Upset by Hair Loss: Week 97(n=0, 0, 1, 0)	88888 (± 88888)	88888 (± 88888)	0.0 (± 99999)	88888 (± 88888)

Upset by Hair Loss: Week 109(n=0, 0, 2, 0)	88888 (± 88888)	88888 (± 88888)	0.0 (± 0.0)	88888 (± 88888)
Upset by Hair Loss: Week 121(n=0, 0, 0, 0)	88888 (± 88888)	88888 (± 88888)	88888 (± 88888)	88888 (± 88888)

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Positive Androgen Receptor (AR) Expression by Immunohistochemistry (IHC)[15]

End point description:

Protocol of this study was amended and data for this endpoint was not analysed as per planned analysis.

End point type	Other pre-specified

End point timeframe:

Day 1, 29, 57, 113 and 169

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[16]	0[17]	0[18]	0[19]
Units: Participants				

Notes:

[16] - Protocol was amended and data for this endpoint was not analysed as per planned analysis.

[17] - Protocol was amended and data for this endpoint was not analysed as per planned analysis.

[18] - Protocol was amended and data for this endpoint was not analysed as per planned analysis.

[19] - Protocol was amended and data for this endpoint was not analysed as per planned analysis.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[20]

End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following endpoints 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 participants 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 (approximately up to 10.13 years)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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: Participants				
AEs	59	58	58	53
SAEs	14	13	10	8

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Clinically Significant Vital Sign Abnormalities[21]

End point description:

Criteria for clinically significant vital sign abnormalities: 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 SBP >=140 mmHg, most extreme post-baseline 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, most extreme post-baseline DBP >=90 mmHg, most extreme post-baseline DBP >=105 mmHg, most extreme DBP >=90 mmHg and >=15 mmHg CFB, most extreme DBP >=105 mmHg and >=15 mmHg CFB; heart rate <50 beats per minute (BPM) and DFB >20 BPM or heart rate >120 BPM and IFB >30 BPM. Safety population was analysed in this endpoint.

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 (approximately up to 10.13 years)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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: Participants				
Blood pressure	38	39	43	25
Heart rate	0	2	0	0

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Treatment-Emergent Adverse Events of Grade 3 or Higher Severity[22]

End point description:

An AE was any untoward medical occurrence in a participant 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 participants with treatment-emergent AEs of grade 3 (severe) or higher grade were reported in this endpoint. Safety population included all the participants 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 (approximately up to 10.13 years)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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: Participants	21	16	22	12

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression Free Survival (PFS): Stratified Analyses By

Electronic Data Capture (EDC)

End point title	Progression Free Survival (PFS): Stratified Analyses By Electronic Data Capture (EDC)[23]

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 according to RECIST 1.1= >=20 % increase in sum of diameters of target lesions taking as reference smallest sum recorded since start of treatment/unequivocal progression in non-target lesions or appearance >=1 lesion. PFS was analysed based on investigator assessment of disease progression. Participants who were not known to have had PFS event at analysis date were censored at last tumor assessment date prior to data cutoff/start date of new therapy, whichever occurred first. Analysis was performed on all randomized participants. Randomization to cohort was based on participant's exposure to advance setting hormonal therapy. Initial randomization was done by IWRS. Later, upon detailed data entry in EDC, it was determined 1 participant was incorrectly assigned to Cht1:Enz+Exe by IWRS, hence counted in Cht2:Enz+Exe 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 3 years)

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	64	60	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	PFS: By Electronic Data Capture (EDC)
Comparison groups	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg v Double blind Cohort 2: Placebo + Exemestane 25 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other[24]
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

Notes:

[24] - Hazard ratio was based on stratified Cox regression model.

Statistical analysis title	PFS: By Electronic Data Capture (EDC)
Comparison groups	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg v Double blind Cohort 1: Placebo + Exemestane 25 mg
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

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

End point title	Number of Participants With Clinically Significant Laboratory Abnormalities[25]

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 participants 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 3 years)

Notes:

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

Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind 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: Participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

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

End point title	Progression Free Survival (PFS): Diagnostic Positive (DX+) Population Stratified Analyses By Electronic Data Capture (EDC)[26]

End point description:

PFS: time from randomization to first documentation of PD or death on study due to any cause, whichever occurred first. PD per RECIST 1.1: >= 20% increase in sum of diameters of target lesions taking as reference smallest sum recorded since start of treatment or unequivocal progression in non-target lesions or appearance of 1 or more new lesions. The analysis of PFS was based on investigator assessment of disease progression. Participants who were not known to have had a 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 the first unblinded analysis as meeting the threshold for diagnostic score based on ribonucleic acid (RNA) sequencing data from tumor tissue. "Subjects Analyzed" =participants evaluable for this endpoint. Here, 99999=Upper limit of 95% CI not reached due to insufficient number of participants with events.

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)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting groups specific to this endpoint are included.

End point values	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 1: Placebo + Exemestane 25 mg	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg	Double blind Cohort 2: Placebo + Exemestane 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
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	DX+ Population By Electronic Data Capture (EDC)
Comparison groups	Double blind Cohort 1: Enzalutamide 160 mg + Exemestane 50 mg v Double blind Cohort 1: Placebo + Exemestane 25 mg

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	DX+ Population By Electronic Data Capture (EDC)
Comparison groups	Double blind Cohort 2: Enzalutamide 160 mg + Exemestane 50 mg v Double blind Cohort 2: Placebo + Exemestane 25 mg
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[27]
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

Notes:

[27] - Hazard ratio was based on stratified Cox regression model.

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 10.13 years)

Adverse event reporting additional description:

Same event may appear as both an adverse event (AE) and a serious AE, but they are distinct events. Event may be categorized as serious in one participant and as non-serious in another, or one may have experienced both serious and non-serious event during study. AEs and all-cause mortality were collected and evaluated 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:

Participants 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. Participants 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:

Participants 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. Participants 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:

Participants 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 participants 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. Participants 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:

Participants 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 participants 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. Participants 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 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 62 (22.58%)	10 / 60 (16.67%)	8 / 60 (13.33%)

number of deaths (all causes)	2	3	2
number of deaths resulting from adverse events	2	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA PANCREAS			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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 METASTATIC			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
BREAST CANCER			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
METASTATIC PAIN			
subjects affected / exposed	1 / 62 (1.61%)	1 / 60 (1.67%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONTRALATERAL BREAST CANCER			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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%)	0 / 60 (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
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
PLASMA CELL MYELOMA			

subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
MALIGNANT ASCITES			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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			
PAIN			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
DISEASE PROGRESSION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
ASTHENIA			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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 / 60 (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
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
FATIGUE			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
FACIAL PAIN			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
ANAPHYLACTIC REACTION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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

PLEURAL EFFUSION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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			
SUICIDAL IDEATION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
DELIRIUM			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
HUMERUS FRACTURE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
LACERATION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
RADIATION PNEUMONITIS			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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

TRAUMATIC HAEMORRHAGE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
OPTIC NERVE INJURY			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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%)	1 / 60 (1.67%)	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 / 60 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
BRACHIAL PLEXOPATHY			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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

SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
SYNCOPE			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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 / 60 (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
GRAND MAL CONVULSION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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%)	1 / 60 (1.67%)	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
INTRACRANIAL HAEMATOMA			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
SPEECH DISORDER			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
Blood and lymphatic system disorders			
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
ANAEMIA			

subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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 disorders			
FAECES DISCOLOURED			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
OESOPHAGEAL STENOSIS			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
VOMITING			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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%)	1 / 60 (1.67%)	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
Hepatobiliary disorders			
HEPATIC HAEMORRHAGE			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
CHOLECYSTITIS			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
PATHOLOGICAL FRACTURE			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
NECK PAIN			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
MASTICATION DISORDER			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
Infections and infestations			
BREAST CELLULITIS			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
PNEUMONIA			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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

WOUND INFECTION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
PYELONEPHRITIS			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 62 (0.00%)	0 / 60 (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
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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%)	2 / 60 (3.33%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOPHOSPHATAEMIA			
subjects affected / exposed	1 / 62 (1.61%)	0 / 60 (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
HYPONATRAEMIA			
subjects affected / exposed	0 / 62 (0.00%)	1 / 60 (1.67%)	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

Serious adverse events	Cohort 1: Placebo + Exemestane 25 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 63 (20.63%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA PANCREAS			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BREAST CANCER METASTATIC			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BREAST CANCER			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
METASTATIC PAIN			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CONTRALATERAL BREAST CANCER			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LYMPHANGIOSIS CARCINOMATOSA			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MALIGNANT PLEURAL EFFUSION			

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PLASMA CELL MYELOMA				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
METASTASES TO CENTRAL NERVOUS SYSTEM				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MALIGNANT ASCITES				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
PAIN				
subjects affected / exposed	0 / 63 (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 / 63 (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 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DISEASE PROGRESSION				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			
ASTHENIA				

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHILLS				
subjects affected / exposed	0 / 63 (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 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FATIGUE				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FACIAL PAIN				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
DRUG HYPERSENSITIVITY				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ANAPHYLACTIC REACTION				
subjects affected / exposed	0 / 63 (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 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

DYSPNOEA EXERTIONAL				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PLEURAL EFFUSION				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
SUICIDAL IDEATION				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DELIRIUM				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
FALL				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HUMERUS FRACTURE				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
LACERATION				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

RADIATION PNEUMONITIS				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TRAUMATIC HAEMORRHAGE				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
OPTIC NERVE INJURY				
subjects affected / exposed	0 / 63 (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 / 63 (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	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
DIZZINESS				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CEREBROVASCULAR ACCIDENT				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BRACHIAL PLEXOPATHY				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

HAEMORRHAGE INTRACRANIAL				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			
SPINAL CORD COMPRESSION				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SYNCOPE				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
EMBOLIC STROKE				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GRAND MAL CONVULSION				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
STATUS EPILEPTICUS				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INTRACRANIAL HAEMATOMA				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SPEECH DISORDER				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				

THROMBOCYTOPENIA			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ANAEMIA			
subjects affected / exposed	0 / 63 (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	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
OESOPHAGEAL STENOSIS			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VOMITING			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
HEPATIC HAEMORRHAGE			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

CHOLECYSTITIS			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 63 (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 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PATHOLOGICAL FRACTURE			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
NECK PAIN			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MASTICATION DISORDER			
subjects affected / exposed	0 / 63 (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 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
WOUND INFECTION				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PYELONEPHRITIS				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
URINARY TRACT INFECTION				
subjects affected / exposed	0 / 63 (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 / 63 (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 / 63 (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	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HYPOPHOSPHATAEMIA				

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HYPONATRAEMIA			
subjects affected / exposed	0 / 63 (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 2: Enzalutamide 160 mg + Exemestane 50 mg	Cohort 2: Placebo + Exemestane 25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 62 (95.16%)	57 / 60 (95.00%)	52 / 60 (86.67%)
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 62 (0.00%)	2 / 60 (3.33%)	3 / 60 (5.00%)
occurrences (all)	0	3	3
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 62 (0.00%)	2 / 60 (3.33%)	4 / 60 (6.67%)
occurrences (all)	0	3	5
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	19 / 62 (30.65%)	14 / 60 (23.33%)	9 / 60 (15.00%)
occurrences (all)	21	19	10
HYPERTENSION			
subjects affected / exposed	8 / 62 (12.90%)	2 / 60 (3.33%)	1 / 60 (1.67%)
occurrences (all)	9	2	1
Nervous system disorders			
AMNESIA			
subjects affected / exposed	4 / 62 (6.45%)	1 / 60 (1.67%)	1 / 60 (1.67%)
occurrences (all)	4	1	1
DIZZINESS			
subjects affected / exposed	7 / 62 (11.29%)	5 / 60 (8.33%)	2 / 60 (3.33%)
occurrences (all)	8	5	2

HEADACHE			
subjects affected / exposed	9 / 62 (14.52%)	9 / 60 (15.00%)	10 / 60 (16.67%)
occurrences (all)	10	12	18
NEUROPATHY PERIPHERAL			
subjects affected / exposed	4 / 62 (6.45%)	0 / 60 (0.00%)	1 / 60 (1.67%)
occurrences (all)	4	0	1
PARAESTHESIA			
subjects affected / exposed	4 / 62 (6.45%)	2 / 60 (3.33%)	2 / 60 (3.33%)
occurrences (all)	5	2	2
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	9 / 62 (14.52%)	6 / 60 (10.00%)	4 / 60 (6.67%)
occurrences (all)	9	9	8
FATIGUE			
subjects affected / exposed	24 / 62 (38.71%)	21 / 60 (35.00%)	13 / 60 (21.67%)
occurrences (all)	31	24	17
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 62 (6.45%)	6 / 60 (10.00%)	3 / 60 (5.00%)
occurrences (all)	11	8	9
Gastrointestinal disorders			
VOMITING			
subjects affected / exposed	11 / 62 (17.74%)	6 / 60 (10.00%)	3 / 60 (5.00%)
occurrences (all)	17	8	4
CONSTIPATION			
subjects affected / exposed	11 / 62 (17.74%)	8 / 60 (13.33%)	8 / 60 (13.33%)
occurrences (all)	11	10	9
DYSPEPSIA			
subjects affected / exposed	1 / 62 (1.61%)	5 / 60 (8.33%)	4 / 60 (6.67%)
occurrences (all)	1	5	4
NAUSEA			
subjects affected / exposed	24 / 62 (38.71%)	18 / 60 (30.00%)	11 / 60 (18.33%)
occurrences (all)	33	23	17
DIARRHOEA			
subjects affected / exposed	14 / 62 (22.58%)	7 / 60 (11.67%)	11 / 60 (18.33%)
occurrences (all)	18	9	16

ABDOMINAL PAIN			
subjects affected / exposed	1 / 62 (1.61%)	2 / 60 (3.33%)	4 / 60 (6.67%)
occurrences (all)	1	2	5
ABDOMINAL PAIN UPPER			
subjects affected / exposed	3 / 62 (4.84%)	4 / 60 (6.67%)	2 / 60 (3.33%)
occurrences (all)	4	4	3
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	10 / 62 (16.13%)	2 / 60 (3.33%)	4 / 60 (6.67%)
occurrences (all)	11	2	5
DYSPNOEA			
subjects affected / exposed	9 / 62 (14.52%)	5 / 60 (8.33%)	4 / 60 (6.67%)
occurrences (all)	10	7	5
OROPHARYNGEAL PAIN			
subjects affected / exposed	4 / 62 (6.45%)	1 / 60 (1.67%)	0 / 60 (0.00%)
occurrences (all)	4	1	0
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	8 / 62 (12.90%)	5 / 60 (8.33%)	2 / 60 (3.33%)
occurrences (all)	9	5	2
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	5 / 62 (8.06%)	5 / 60 (8.33%)	4 / 60 (6.67%)
occurrences (all)	5	5	4
ANXIETY			
subjects affected / exposed	6 / 62 (9.68%)	2 / 60 (3.33%)	1 / 60 (1.67%)
occurrences (all)	7	2	1
DEPRESSED MOOD			
subjects affected / exposed	1 / 62 (1.61%)	4 / 60 (6.67%)	0 / 60 (0.00%)
occurrences (all)	3	4	0
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	7 / 62 (11.29%)	3 / 60 (5.00%)	3 / 60 (5.00%)
occurrences (all)	9	4	3
BONE PAIN			

subjects affected / exposed	3 / 62 (4.84%)	5 / 60 (8.33%)	2 / 60 (3.33%)
occurrences (all)	3	6	4
BACK PAIN			
subjects affected / exposed	11 / 62 (17.74%)	4 / 60 (6.67%)	11 / 60 (18.33%)
occurrences (all)	12	5	13
ARTHRALGIA			
subjects affected / exposed	15 / 62 (24.19%)	10 / 60 (16.67%)	7 / 60 (11.67%)
occurrences (all)	18	11	9
MYALGIA			
subjects affected / exposed	4 / 62 (6.45%)	0 / 60 (0.00%)	4 / 60 (6.67%)
occurrences (all)	4	0	6
MUSCULOSKELETAL PAIN			
subjects affected / exposed	7 / 62 (11.29%)	2 / 60 (3.33%)	2 / 60 (3.33%)
occurrences (all)	8	3	4
PAIN IN EXTREMITY			
subjects affected / exposed	4 / 62 (6.45%)	3 / 60 (5.00%)	5 / 60 (8.33%)
occurrences (all)	6	5	6
Infections and infestations			
INFLUENZA			
subjects affected / exposed	3 / 62 (4.84%)	1 / 60 (1.67%)	2 / 60 (3.33%)
occurrences (all)	4	1	2
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	4 / 62 (6.45%)	1 / 60 (1.67%)	3 / 60 (5.00%)
occurrences (all)	4	1	5
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 62 (3.23%)	1 / 60 (1.67%)	4 / 60 (6.67%)
occurrences (all)	3	1	9
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	6 / 62 (9.68%)	6 / 60 (10.00%)	2 / 60 (3.33%)
occurrences (all)	9	7	2

Non-serious adverse events	Cohort 1: Placebo + Exemestane 25 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 63 (90.48%)		

Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	14 / 63 (22.22%)		
occurrences (all)	16		
HYPERTENSION			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Nervous system disorders			
AMNESIA			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
DIZZINESS			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
HEADACHE			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	6		
NEUROPATHY PERIPHERAL			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
PARAESTHESIA			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	7		
FATIGUE			

subjects affected / exposed occurrences (all)	23 / 63 (36.51%) 26		
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	 1 / 63 (1.59%) 1		
Gastrointestinal disorders VOMITING subjects affected / exposed occurrences (all) CONSTIPATION subjects affected / exposed occurrences (all) DYSPEPSIA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) ABDOMINAL PAIN subjects affected / exposed occurrences (all) ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	 7 / 63 (11.11%) 12 7 / 63 (11.11%) 7 6 / 63 (9.52%) 6 10 / 63 (15.87%) 11 10 / 63 (15.87%) 10 2 / 63 (3.17%) 2 2 / 63 (3.17%) 2		
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) DYSPNOEA subjects affected / exposed occurrences (all) OROPHARYNGEAL PAIN	 8 / 63 (12.70%) 10 8 / 63 (12.70%) 9		

subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
ANXIETY			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
DEPRESSED MOOD			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
BONE PAIN			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
BACK PAIN			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	7		
ARTHRALGIA			
subjects affected / exposed	11 / 63 (17.46%)		
occurrences (all)	16		
MYALGIA			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	2		
PAIN IN EXTREMITY			

subjects affected / exposed occurrences (all)	8 / 63 (12.70%) 13		
Infections and infestations INFLUENZA subjects affected / exposed occurrences (all) UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all) URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	 4 / 63 (6.35%) 7 1 / 63 (1.59%) 1 3 / 63 (4.76%) 5		
Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all)	 6 / 63 (9.52%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2024	A secondary immunogenicity objective in response to a regulatory (CBER) request was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported