Clinical trial results:
An Open-label Randomised Phase 2 Trial of Amcenestrant (SAR439859), Versus Endocrine Monotherapy as per Physician's Choice in Patients With Estrogen Receptor-positive, HER2-negative Locally advanced or Metastatic breast cancer With Prior exposure to Hormonal Therapies

Summary

EudraCT number	2018-004593-98
Trial protocol	SE PL ES GR CZ LV IT
Global end of trial date	02 January 2025

Results information

Result version number	v2
This version publication date	07 January 2026
First version publication date	15 April 2023
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	ACT16105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04059484
WHO universal trial number (UTN)	U1111-1217-2774
Other trial identifiers	IND: 133204

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 Avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	16 January 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 January 2025
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether amcenestrant 400 milligrams (mg) per os improves progression-free survival (PFS) when compared with an endocrine monotherapy of the choice of the physician, in participants with metastatic or locally advanced breast cancer.

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the participant and considering the local culture. During the course of the trial, participants were provided with individual participant cards indicating the nature of the trial the participant is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 October 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 22
Country: Number of subjects enrolled	Argentina: 25
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	China: 90
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Japan: 15
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 20
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	Türkiye: 13
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Spain: 9

Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Latvia: 4
Worldwide total number of subjects	367
EEA total number of subjects	71

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)	251
From 65 to 84 years	115
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

367 participants were screened in main (global) cohort,77 were screen failures (not meeting eligibility criteria). As pre-specified in protocol, Chinese participants from main cohort and China cohort were pooled for purpose of analysis of Chinese cohort. 90 participants (including 13 participants from main cohort) were randomized in Chinese cohort.

Pre-assignment

Screening details:

Total 367 unique participants enrolled:290 participants (main cohort), 77 new participants (Chinese cohort). Study was terminated as it did not meet primary objective of improved progression free survival with amcenestrant versus endocrine treatment of physician's choice.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort

Arm description:

Participants received potential control treatment of the choice of the physician depending on each participant’s medical condition and in accordance with the approved label. Control treatment included one of the following treatments to be selected before randomization and used as monotherapy: 1) Fulvestrant 500 mg, given as two 5-milliliters (mL) intramuscular (IM) injections on Cycle 1 Days 1 and 15, and at Day 1 of each 28-day treatment cycle thereafter; or 2) Aromatase inhibitors (anastrozole 1 mg or letrozole 2.5 mg or exemestane 25 mg) orally (PO), once a day (QD); or 3) Tamoxifen 20 mg/day PO, QD or twice a day (maximum exposure: 116 weeks).

Arm type	Active comparator
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	Faslodex®
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant 500 mg given as two 250 mg (5 mL) IM injections on Cycle 1 Days 1 and 15, and at Day 1 of each 28-day treatment cycle thereafter.

Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	Nolvadex®/Tamoxifen Generics
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tamoxifen 20 mg PO QD or 10 mg twice a day PO, approximately at the same time every day regardless of food status.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	Aromasin®/Exemestane Generics
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane 25 mg PO, QD approximately at the same time every day after a meal.

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	Arimidex®/Anastrozole Generics
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Anastrozole 1 mg PO, QD approximately at the same time every day regardless of food status.

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	Femara®/Letrozole Generics
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole 2.5 mg PO, QD approximately at the same time every day regardless of food status.

Arm title	Amcenestrant- Main Cohort

Arm description:

Participants received 4 capsules of 100 mg, amcenestrant PO, QD from Day 1 to Day 28 in each 28-day treatment cycle until precluded by unacceptable toxicity or disease progression or participant’s request to stop treatment or Investigator decision, whichever occurred first (maximum exposure: 116 weeks).

Arm type	Experimental
Investigational medicinal product name	Amcenestrant
Investigational medicinal product code	SAR439859
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Amcenestrant (4 capsules of 100 mg) PO, QD from Day 1 to Day 28 in each 28-day treatment cycle in the morning with or without food, at approximately the same time every day.

Arm title	Physician Choice Endocrine Monotherapy (PCEM)- Chinese Cohort

Arm description:

Participants received potential control treatment of the choice of the physician depending on each participant's medical condition and in accordance with the approved label. Control treatment included one of the following treatments to be selected before randomization and used as monotherapy: 1) Fulvestrant 500 mg, given as two 5-mL IM injections on Cycle 1 Days 1 and 15, and at Day 1 of each 28-day treatment cycle thereafter; or 2) Aromatase inhibitors (anastrozole 1 mg or letrozole 2.5 mg or exemestane 25 mg) PO, QD; or 3) Tamoxifen 20 mg/day PO, QD or twice a day (maximum treatment exposure: 183 weeks).

Arm type	Active comparator
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	Faslodex®
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant 500 mg given as two 250 mg (5 mL) IM injections on Cycle 1 Days 1 and 15, and at Day 1 of each 28-day treatment cycle thereafter.

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	Arimidex®/Anastrozole Generics
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Anastrozole 1 mg PO, QD approximately at the same time every day regardless of food status.

Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	Nolvadex®/Tamoxifen Generics
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tamoxifen 20 mg PO QD or 10 mg twice a day PO, approximately at the same time every day regardless of food status.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	Aromasin®/Exemestane Generics
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane 25 mg PO, QD approximately at the same time every day after a meal.

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	Femara®/Letrozole Generics
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole 2.5 mg PO, QD approximately at the same time every day regardless of food status.

Arm title	Amcenestrant- Chinese Cohort

Arm description:

Participants received 4 capsules of 100 mg, amcenestrant PO, QD from Day 1 to Day 28 in each 28-day treatment cycle until precluded by unacceptable toxicity or disease progression or participant's request to stop treatment or Investigator decision, whichever occurred first (maximum treatment exposure: 183 weeks).

Arm type	Experimental
Investigational medicinal product name	Amcenestrant
Investigational medicinal product code	SAR439859
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Amcenestrant (4 capsules of 100 mg) PO, QD from Day 1 to Day 28 in each 28-day treatment cycle in the morning with or without food, at approximately the same time every day.

Number of subjects in period 1	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant- Main Cohort	Physician Choice Endocrine Monotherapy (PCEM)- Chinese Cohort
Started	147	143	42
Completed	0	0	0
Not completed	147	143	42
Consent withdrawn by subject	6	3	1
Adverse event, non-fatal	2	5	-
Not related to Coronavirus Disease-2019 (COVID-19)	19	17	7

Related to COVID-19	-	-	-
Poor compliance to protocol	-	-	1
Progressive disease	120	118	33

Number of subjects in period 1	Amcenestrant-Chinese Cohort
Started	48
Completed	0
Not completed	48
Consent withdrawn by subject	4
Adverse event, non-fatal	1
Not related to Coronavirus Disease-2019 (COVID-19)	10
Related to COVID-19	1
Poor compliance to protocol	-
Progressive disease	32

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
All participants in the study were included in this arm.	

Reporting group values	Overall Study	Total	
Number of subjects	367	367	
Age categorical Units: participants			
Age Continuous Units: years			
arithmetic mean	57.7		
standard deviation	± 12.1	-	
Sex: Female, Male Units: participants			
Female	365	365	
Male	2	2	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	143	143	
Native Hawaiian or Other Pacific Islander	2	2	
Black or African American	0	0	
White	204	204	
More than one race	2	2	
Unknown or Not Reported	16	16	

End points

End points reporting groups

Reporting group title	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort

Reporting group description:

Participants received potential control treatment of the choice of the physician depending on each participant’s medical condition and in accordance with the approved label. Control treatment included one of the following treatments to be selected before randomization and used as monotherapy: 1) Fulvestrant 500 mg, given as two 5-milliliters (mL) intramuscular (IM) injections on Cycle 1 Days 1 and 15, and at Day 1 of each 28-day treatment cycle thereafter; or 2) Aromatase inhibitors (anastrozole 1 mg or letrozole 2.5 mg or exemestane 25 mg) orally (PO), once a day (QD); or 3) Tamoxifen 20 mg/day PO, QD or twice a day (maximum exposure: 116 weeks).

Reporting group title	Amcenestrant- Main Cohort

Reporting group description:

Participants received 4 capsules of 100 mg, amcenestrant PO, QD from Day 1 to Day 28 in each 28-day treatment cycle until precluded by unacceptable toxicity or disease progression or participant’s request to stop treatment or Investigator decision, whichever occurred first (maximum exposure: 116 weeks).

Reporting group title	Physician Choice Endocrine Monotherapy (PCEM)- Chinese Cohort

Reporting group description:

Participants received potential control treatment of the choice of the physician depending on each participant's medical condition and in accordance with the approved label. Control treatment included one of the following treatments to be selected before randomization and used as monotherapy: 1) Fulvestrant 500 mg, given as two 5-mL IM injections on Cycle 1 Days 1 and 15, and at Day 1 of each 28-day treatment cycle thereafter; or 2) Aromatase inhibitors (anastrozole 1 mg or letrozole 2.5 mg or exemestane 25 mg) PO, QD; or 3) Tamoxifen 20 mg/day PO, QD or twice a day (maximum treatment exposure: 183 weeks).

Reporting group title	Amcenestrant- Chinese Cohort

Reporting group description:

Participants received 4 capsules of 100 mg, amcenestrant PO, QD from Day 1 to Day 28 in each 28-day treatment cycle until precluded by unacceptable toxicity or disease progression or participant's request to stop treatment or Investigator decision, whichever occurred first (maximum treatment exposure: 183 weeks).

Primary: Progression free survival (PFS)

End point title	Progression free survival (PFS)[1]

End point description:

PFS is defined as the time in months interval from the date of randomization to the date of first documented tumor progression as per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) assessed by independent central review (ICR) or death (due to any cause), whichever comes first. Progressive Disease (PD) as per RECIST 1.1: at least a 20 percent (%) increase in sum of diameters of target lesions, unequivocal progression of existing non-target lesions. Analysis was performed by Kaplan-Meier method. Analysis was performed on the ITT population which consist of all participants from the enrolled population (with a signed informed consent form) who have been allocated a randomization number by the Interactive Response Technology (IRT).

End point type	Primary

End point timeframe:

From randomization to the date of first documented tumor progression or death due to any cause or data cut-off date whichever comes first (maximum duration: 116 weeks)

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: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant- Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	143		
Units: months				
median (confidence interval 95%)	3.7 (2.0 to 4.9)	3.6 (2.0 to 3.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Progression Free Survival

Statistical analysis description:

A hierarchical testing procedure was used to ensure a strong control of the overall Type I error. Testing was then performed sequentially in order the outcome measures was reported and continued when previous outcome measure was statistically significant at one-sided 2.5% for the primary and the first secondary outcome. Here, ECOG=Eastern Cooperative Oncology Group.

Comparison groups	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort v Amcenestrant- Main Cohort
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6437 [2]
Method	Stratified Log-Rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.789
upper limit	1.4

Notes:

[2] - One-sided p-value based on Stratified log-rank test. Threshold for statistical significance at 0.025. Stratified on presence of visceral metastasis, prior treatment with cyclin-dependent kinase 4/6 inhibitors and ECOG according to IRT.

Primary: Chinese Cohort: Progression Free Survival

End point title	Chinese Cohort: Progression Free Survival[3][4]

End point description:

PFS is defined as the time in months interval from the date of randomization to the date of first documented tumor progression as per RECIST 1.1 assessed by ICR or death (due to any cause), whichever comes first. PD as per RECIST 1.1: at least a 20% increase in sum of diameters of target lesions, unequivocal progression of existing non-target lesions. Analysis was performed by Kaplan-Meier method. Analysis was performed on the ITT population. Here, '99999' is used as a space filler and denotes that median and upper limit of 95% confidence interval (CI) were not estimable due to insufficient number of participants with events at study termination.

End point type	Primary

End point timeframe:

From randomization to the date of first documented tumor progression or death due to any cause or data cut-off date whichever comes first, up to primary completion date of 15-Feb-2022, a maximum of 121 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint was descriptive in nature, no statistical analysis is reported.

[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: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Chinese Cohort	Amcenestrant- Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	48		
Units: months				
median (confidence interval 95%)	99999 (3.7 to 99999)	7.2 (3.7 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response

End point title	Percentage of Participants With Objective Response[5]

End point description:

Objective response is defined as percentage of participants having a partial response (PR) or complete response (CR) according to the RECIST version 1.1 assessed by ICR. As per RECIST 1.1, CR was defined as disappearance of all target and non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<) 10 millimeters (mm). PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Analysis was performed on the ITT population.

End point type	Secondary

End point timeframe:

From randomization to the date of first documented tumor progression, death due to any cause or data cut-off date whichever comes first (maximum duration: 116 weeks)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant- Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	143		
Units: percentage of participants				
number (confidence interval 95%)	8.8 (4.8 to 14.6)	11.9 (7.1 to 18.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)[6]

End point description:

OS is defined as the time interval from the date of randomization to the date of documented death (due to any cause). In the absence of observation of death, survival time was censored to last date the participant is known to be alive or at the cut-off date, whichever comes first. Analysis was performed by Kaplan-Meier method. Analysis was performed on the ITT population. Here, '99999' is used as a space filler and denotes that median and upper limit of 95% CI were not estimable due to the smaller number of participants with events.

End point type	Secondary

End point timeframe:

From randomization to the death due to any cause or data cut-off date whichever comes first (maximum duration: 116 weeks)

Notes:

[6] - 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: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant-Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	143		
Units: months				
median (confidence interval 95%)	99999 (18.9 to 99999)	99999 (21.5 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Control

End point title	Percentage of Participants With Disease Control[7]

End point description:

Disease control is defined as percentage of participants having a confirmed CR, PR, or stable disease (SD) or Non-CR/Non-PD as BOR determined by ICR as per RECIST 1.1 from the date of randomization to the date of end of treatment. As per RECIST 1.1, CR: disappearance of all target and non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: at least a 30% decrease in sum of diameters of target lesions, taking as reference baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest

sum diameters. Non-CR/Non-PD: persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits. PD: at least 20% increase in sum of diameters of target lesions, unequivocal progression of existing non-target lesions. ITT population.

End point type	Secondary

End point timeframe:

From randomization to the date of first documented tumor progression, death due to any cause or data cut-off date whichever comes first (maximum duration: 116 weeks)

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: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant-Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	143		
Units: percentage of participants				
number (confidence interval 95%)	53.7 (45.3 to 62.0)	54.5 (46.0 to 62.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)[8]

End point description:

DOR:time(in months) from first documented evidence of CR or PR until progressive disease(PD)determined by ICR as per RECIST 1.1 or death from any cause, whichever occurs first.For participants with ongoing response at time of analysis,DOR was censored at date of last valid disease assessment not showing documented progression performed before the initiation of a new anticancer treatment(if any).As per RECIST 1.1,CR:disappearance of all target and non-target lesions and normalization of tumor marker level.Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to <10 mm.PR:at least a 30% decrease in the sum of diameters of target lesions, taking as reference baseline sum diameters.PD:at least 20% increase in sum of diameters of target lesions,unequivocal progression of existing non-target lesions.Analyzed on subset of participants with objective response.99999:median & 95% CI upper limit not estimable due to less number of participants with events.

End point type	Secondary

End point timeframe:

From the date of first response to the date of first documented tumor progression, death due to any cause or data cut-off date whichever comes first (maximum duration: 116 weeks)

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: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant-Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	17		
Units: months				
median (confidence interval 95%)	99999 (3.9 to 99999)	15.1 (5.6 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) According to Estrogen Receptor 1 Gene (ESR1) Mutation Status

End point title	Progression Free Survival (PFS) According to Estrogen Receptor 1 Gene (ESR1) Mutation Status[9]

End point description:

PFS:time(in months) from randomization to date of first documented tumor progression per RECIST 1.1 assessed by ICR or death(due to any cause), whichever comes first.Progression as per RECIST 1.1:at least a 20 percent (%) increase in sum of diameters of target lesions,unequivocal progression of existing non-target lesions.Mutation status(wild type, mutant) of twelve specific mutations of ESR1 gene was determined by multiplex droplet digital polymerase chain reaction (ddPCR), including their mutant frequency and concentration. PFS is reported based on ESR1 mutation status of participants:wild type and mutants.ESR1:gene encoding estrogen receptor alpha.ESR1 mutant type breast cancer:disease where ESR1 gene had a mutation(i.e., type of error). ESR1 wild type breast cancer:disease where ESR1 gene was normal without mutation. Kaplan-Meier method. ITT population.'Number of subjects analyzed' & 'n' = participants with available data for this endpoint & each specified category, respectively.

End point type	Secondary

End point timeframe:

From randomization to the date of first documented tumor progression, death due to any cause or data cut-off date whichever comes first (maximum duration: 116 weeks)

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: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant-Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	140		
Units: months				
median (confidence interval 95%)				
Mutated (n = 55, 65)	2.0 (1.9 to 4.3)	3.7 (1.9 to 7.2)		
Wild type (n = 85, 75)	3.9 (3.6 to 9.2)	3.5 (2.0 to 3.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Benefit

End point title	Percentage of Participants With Clinical Benefit[10]

End point description:

Clinical Benefit is defined as percentage of participants having a confirmed CR, PR, SD, or Non-CR/Non-PD for at least 24 weeks determined by ICR as per RECIST 1.1 from the date of randomization to the date of end of treatment. As per RECIST 1.1, CR: disappearance of all target and non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters. Non-CR/Non-PD: persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits. PD:at least 20% increase in sum of diameters of target lesions, unequivocal progression of existing non-target lesions. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomization to the date of first documented tumor progression, death due to any cause or data cut-off date whichever comes first (maximum duration: 116 weeks)

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: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant- Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	143		
Units: percentage of participants				
number (confidence interval 95%)	29.3 (22.0 to 37.3)	27.3 (20.2 to 35.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Plasma Concentrations of Amcenestrant

End point title	Pharmacokinetics: Plasma Concentrations of Amcenestrant[11]

End point description:

Amcenestrant plasma concentrations at specified time points are reported. Analysis was performed on pharmacokinetic-evaluable population: all participants who were assigned to study intervention, took at least 1 dose of study intervention and had at least 1 available plasma concentration post treatment with adequate documentation of date and time of dosing and date and time of sampling. Here, 'n' = participants with available data for each specified category.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 1.5 hours(h), 4h post-dose, Day 15: pre-dose, Cycle 2 Day 1: pre-dose, 1.5h, 4h, 8h post-dose, Cycle 3 Day 1: pre-dose, Cycle 4 Day 1: pre-dose, Cycle 6 Day 1: pre-dose

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: Data for this endpoint was not planned to be collected and analyzed for PCEM arm.

End point values	Amcenestrant-Main Cohort			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1: 1.5h (n = 130)	3185.7 (± 3145.2)			
Cycle 1 Day 1: 4h (n = 128)	4753.1 (± 3463.7)			
Cycle 1 Day 15: Pre-dose (n = 87)	516.4 (± 377.2)			
Cycle 2 Day 1: Pre-dose (n = 98)	479.1 (± 320.3)			
Cycle 2 Day 1: 1.5h (n = 121)	2719.6 (± 2374.0)			
Cycle 2 Day 1: 4h (n = 115)	3801.8 (± 2370.8)			
Cycle 2 Day 1: 8h (n = 98)	2303.8 (± 1411.4)			
Cycle 3 Day 1: Pre-dose (n = 42)	593.6 (± 815.1)			
Cycle 4 Day 1: Pre-dose (n = 44)	661.5 (± 860.5)			
Cycle 6 Day 1: Pre-dose (n = 28)	531.5 (± 468.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Within-Participant Steady State Ctrough of Amcenestrant

End point title	Within-Participant Steady State Ctrough of Amcenestrant[12]

End point description:

Within-participant Steady state Ctrough was defined as the median value of the Ctrough across study using plasma concentration of predose samples at Cycle 1 Day 15 and Day 1 of Cycle 2, 3, 4 and 6 for each individual participant. Average (mean) of all calculated Ctrough values for all participants across study (Cycle 1 Day 15 and Day 1 of Cycle 2, 3, 4 and 6) was derived and reported in this outcome measure. Analysis was performed on Pharmacokinetic-evaluable population. Here, 'number of subjects analyzed' = participants with available data for this endpoint.

End point type	Secondary

End point timeframe:

Predose on Cycle 1 Day 15; Cycle 2 Day 1; Cycle 3 Day 1; Cycle 4 Day 1; Cycle 6 Day 1

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: Data for this endpoint was not planned to be collected and analyzed for PCEM arm.

End point values	Amcenestrant-Main Cohort			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: ng/mL				
arithmetic mean (standard deviation)	491.35 (± 316.51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30) Domain Scores

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30) Domain Scores[13]

End point description:

Cancer-specific instrument with 30 questions for evaluation of new chemotherapy & assessment of participant reported outcome, includes 5 functional scales,9 symptom scales,& Global Health Status/quality of life scale (GHS/QoL).All 14 items/domains scored on scale of 1(not at all) to 4(very much) & GHS/QoL,scored on scale of 1(very poor) to 7(excellent).All scales are transformed from raw scores to linear scales ranging 0 to 100.Higher score for functional & GHS/QoL=higher level of functioning, & higher score for symptoms scales=higher symptom burden. Least Square(LS) mean and Standard Error(SE) are derived from MMRM model with change from Baseline values as response variable,treatment, time,treatment-by-time interaction,Baseline value and stratifications factors as fixed effect.Average of LS mean change from baseline values of overall treatment (i.e., each cycle [Cycle 1 up to Cycle 30]). Safety population evaluable. 'n'=participants with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, overall treatment duration (Cycle 1 up to Cycle 30 [i.e.,116 weeks])

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: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant-Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	143		
Units: score on a scale				
least squares mean (standard error)				
GHS/QoL (n = 130, 125)	1.8 (± 1.6)	2.5 (± 1.6)		
Physical functioning (n = 131, 126)	-1.2 (± 1.3)	-3.1 (± 1.3)		
Role functioning (n = 131, 126)	-2.4 (± 1.9)	-3.0 (± 1.8)		
Emotional functioning (n = 131, 126)	-2.2 (± 1.7)	3.0 (± 1.6)		
Cognitive functioning (n = 131, 126)	-0.9 (± 1.6)	-0.8 (± 1.5)		
Social functioning (n = 130, 126)	-2.5 (± 1.7)	-0.8 (± 1.7)		
Fatigue (n = 131, 126)	1.1 (± 1.9)	2.8 (± 1.9)		

Nausea and vomiting (n = 131, 126)	1.7 (± 1.3)	1.3 (± 1.3)		
Pain (n = 131, 126)	1.1 (± 1.9)	2.1 (± 1.9)		
Dyspnoea (n = 131, 125)	1.0 (± 1.6)	0.8 (± 1.6)		
Insomnia (n = 131, 126)	-1.1 (± 2.3)	-2.3 (± 2.2)		
Appetite loss (n = 130, 126)	2.4 (± 2.3)	1.2 (± 2.3)		
Constipation (n = 131, 126)	-2.3 (± 2.0)	3.0 (± 2.0)		
Diarrhoea (n= 130, 126)	0.3 (± 1.3)	3.9 (± 1.3)		
Financial difficulties (n= 131, 126)	1.7 (± 1.8)	-2.0 (± 1.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions (5D), 5 Levels (5L) (EQ-5D-5L) Score: Health Utility Index Value

End point title	Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions (5D), 5 Levels (5L) (EQ-5D-5L) Score: Health Utility Index Value[14]

End point description:

EQ-5D-5L:consists of 2 sections: EQ-5D-5L health state utility index (descriptive system) & VAS. EQ-5D descriptive system consists of 5 dimensions: mobility,self-care,usual activities,pain/discomfort & anxiety/depression.Each dimension has 5 levels:no problems,slight problems,moderate problems,severe problems,& extreme problems. Response options measured with 5-point Likert scale (for 5L version).EQ-5D-5L responses are converted into single index utility score between 0 to 1,higher score:better health state & lower score indicate worse health state.LS mean and SE are derived from MMRM model with change from Baseline values as response variable, treatment, time, treatment-by-time interaction, Baseline value and stratifications factors as fixed effect. Average of LS mean change from baseline values overall treatment (i.e., each cycle [Cycle 1 up to Cycle 30]) was reported.Safety population evaluable.Here, 'number of subjects analyzed'=participants with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, overall treatment duration (Cycle 1 up to Cycle 30 [i.e.,116 weeks])

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: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant-Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	129		
Units: score on a scale				
least squares mean (standard error)	-0.0 (± 0.0)	-0.0 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions (5D), 5 Levels (5L) (EQ-5D-5L) Score: Visual Analog Scale (VAS) Score

End point title	Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions (5D), 5 Levels (5L) (EQ-5D-5L) Score: Visual Analog Scale (VAS) Score[15]

End point description:

EQ-5D-5L:standardized measure of health status, provides simple, generic measure of health for clinical and economic appraisal, consists of 2 sections: EQ-5D-5L health state utility index (descriptive system) & EQ-5D-5L VAS. VAS designed to rate participant's current health state on a scale from 0 to 100, 0:worst imaginable health state and 100: best imaginable health state. LS mean and SE are derived from MMRM model with change from baseline values as response variable, treatment, time, treatment-by-time interaction, Baseline value and stratifications factors as fixed effect. Average of LS mean change from Baseline values of overall treatment (i.e., each cycle [Cycle 1 up to Cycle 30]) was reported. Safety population evaluable: participants randomly assigned to study intervention, who took at least 1 dose of study intervention, completed Baseline, at least 1 post Baseline on-treatment assessment. Here, 'number of subjects analyzed'=participants with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, overall treatment duration (Cycle 1 up to Cycle 30 [i.e.,116 weeks])

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: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant-Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	125		
Units: score on a scale				
least squares mean (standard error)	0.9 (± 1.4)	0.2 (± 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Breast Cancer Specific Module (EORTC-QLQ-BR23) Domain Scores

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Breast Cancer Specific Module (EORTC-QLQ-BR23) Domain Scores[16]

End point description:

QLQ-BR23:disease-specific Health-related QOL.EORTC-QLQ-BR23 contains 23 items:multi-item scales & single-item measures. 4 functional scales (body image,sexual functioning,sexual enjoyment,future perspective) & 4 scales related to symptoms of disease/treatment (arm symptoms,breast symptoms,systemic therapy side effects,& upset by hair loss).All items scored 1(not at all) to 4(very much).Scores of all scales transformed from raw scores to linear scales ranging 0 to 100.Higher score(functional scales)=better outcome;higher score(symptoms scales)=higher symptom burden.LS mean and SE derived from MMRM model with change from Baseline values as response variable,

treatment-by-time interaction, Baseline value and stratifications factors as fixed effect. Average of LS mean change from baseline values of overall treatment (i.e., each cycle [Cycle 1 up to Cycle 30]) was reported. Safety population evaluable. 'n' = participants with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, overall treatment duration (Cycle 1 up to Cycle 30 [i.e.,116 weeks])

Notes:

[16] - 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: Data for this endpoint was evaluated for Main cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant-Main Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	143		
Units: score on a scale				
least squares mean (standard error)				
Body image (n = 132, 130)	1.8 (± 1.7)	2.2 (± 1.6)		
Sexual functioning (n = 127, 127)	-2.4 (± 1.3)	-2.6 (± 1.2)		
Sexual enjoyment (n = 33, 20)	-1.1 (± 3.0)	0.4 (± 4.1)		
Future perspective (n= 132,130)	10.6 (± 2.7)	12.0 (± 2.6)		
Systemic therapy side effects (n = 133, 130)	0.2 (± 1.0)	0.7 (± 1.0)		
Breast symptoms (n = 129, 128)	-0.4 (± 1.3)	-0.8 (± 1.2)		
Arm symptoms (n = 130, 128)	1.8 (± 1.7)	2.0 (± 1.7)		
Upset by hair loss (n = 37, 47)	-9.7 (± 3.9)	-10.6 (± 3.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Percentage of Participants With Objective Response

End point title	Chinese Cohort: Percentage of Participants With Objective Response[17]

End point description:

Objective response is defined as percentage of participants having a PR or CR according to the RECIST version 1.1 assessed by ICR. As per RECIST 1.1, CR was defined as disappearance of all target and non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Analysis was performed on the ITT population. Only those participants with response are reported.

End point type	Secondary

End point timeframe:

From randomization to the date of first documented tumor progression, death due to any cause or data cut-off date whichever comes first (maximum duration: 183 weeks)

Notes:

[17] - 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: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	46		
Units: percentage of participants				
number (confidence interval 95%)	10.8 (3.0 to 25.4)	6.5 (1.4 to 17.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Overall Survival

End point title	Chinese Cohort: Overall Survival[18]

End point description:

OS is defined as the time interval from the date of randomization to the date of documented death (due to any cause). In the absence of observation of death, survival time was censored to last date the participant is known to be alive or at the cut-off date, whichever comes first. Analysis was performed by Kaplan-Meier method. Analysis was performed on the ITT population. Here, '99999' is used as a space filler and denotes that median, upper and lower limits of 95% CI were not estimable due to insufficient number of participants with events at study termination.

End point type	Secondary

End point timeframe:

From randomization to the death due to any cause or data cut-off date whichever comes first (maximum duration: 183 weeks)

Notes:

[18] - 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: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	48		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Percentage of Participants With Disease Control

End point title	Chinese Cohort: Percentage of Participants With Disease Control[19]

End point description:

Disease control:percentage of participants having a confirmed CR, PR, or SD or Non-CR/Non-PD as BOR determined by ICR as per RECIST 1.1 from date of randomization to date of end of treatment. As per RECIST 1.1, CR:disappearance of all target and non-target lesions and normalization of tumor marker level.Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR:at least a 30% decrease in sum of diameters of target lesions,taking as reference baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters. Non-CR/Non-PD:persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above normal limits. PD:at least 20% increase in sum of diameters of target lesions, unequivocal progression of existing non-target lesions.Analysis was performed on ITT population. Only those participants with response are reported.

End point type	Secondary

End point timeframe:

From randomization to the date of first documented tumor progression, death due to any cause or data cut-off date whichever comes first (maximum duration: 183 weeks)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	46		
Units: percentage of participants				
number (confidence interval 95%)	75.7 (58.8 to 88.2)	73.9 (58.9 to 85.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Percentage of Participants With Clinical Benefit

End point title	Chinese Cohort: Percentage of Participants With Clinical

End point description:

Clinical benefit:percentage of participants having a confirmed CR,PR,SD,or Non-CR/Non-PD for at least 24 weeks determined by ICR as per RECIST 1.1 from date of randomization to date of end of treatment.As per RECIST 1.1,CR:disappearance of all target and non-target lesions and normalization of tumor marker level.Any pathological lymph nodes(whether target/non-target) must have reduction in short axis to <10 mm.PR:at least a 30% decrease in sum of diameters of target lesions,taking as reference the baseline sum diameters.SD:neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD,taking as reference the smallest sum diameters.Non-CR/Non-PD:persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above normal limits.PD:at least 20% increase in sum of diameters of target lesions,unequivocal progression of existing non-target lesions.Analysis was performed on ITT population.Only those participants with response are reported.

End point type	Secondary

End point timeframe:

From randomization to the date of first documented tumor progression, death due to any cause or data cut-off date whichever comes first (maximum duration: 183 weeks)

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: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	46		
Units: percentage of participants				
number (confidence interval 95%)	21.6 (9.8 to 38.2)	23.9 (12.6 to 38.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Progression Free Survival According to Estrogen Receptor 1 Gene Mutation Status

End point title	Chinese Cohort: Progression Free Survival According to Estrogen Receptor 1 Gene Mutation Status[21]

End point description:

PFS:time(in months) interval from date of randomization to date of first documented tumor progression as per RECIST 1.1 assessed by ICR or death(due to any cause), whichever comes first.Progression as per RECIST 1.1:at least a 20% increase in sum of diameters of target lesions, unequivocal progression of existing non-target lesions.Mutation status(wild type,mutant) of twelve specific mutations of ESR1 gene was determined by multiplex ddPCR.PFS is reported based on ESR1 mutation status of participants:wild type and mutants.ESR1:gene encoding estrogen receptor alpha.ESR1 mutant type breast cancer:disease where ESR1 gene had a mutation (type of error).ESR1 wild type breast cancer:disease where ESR1 gene was normal without a mutation. ITT population.'n'= participants with available data for each specified category. '+/-9999':insufficient numbers of participants with 1/2 participants censored prior to any event. '99999': insufficient number of participants with events at study termination.

End point type	Secondary

End point timeframe:

From randomization to the date of first documented tumor progression, death due to any cause or data cut-off date whichever comes first (maximum duration: 183 weeks)

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: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: months				

median (confidence interval 95%)				
Mutated (n = 2, 3)	5.5 (-9999 to 9999)	1.8 (1.7 to 99999)		
Wild type (n = 5, 3)	99999 (1.8 to 99999)	1.9 (1.8 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Duration of Response

End point title	Chinese Cohort: Duration of Response[22]

End point description:

DOR: time (in months) from first documented evidence of CR or PR until PD determined by ICR as per RECIST 1.1 or death from any cause, whichever occurs first. For participants with ongoing response at time of analysis,DOR was censored at the date of last valid disease assessment not showing documented progression performed before initiation of a new anticancer treatment (if any).As per RECIST 1.1,CR:disappearance of all target and non-target lesions and normalization of tumor marker level.Any pathological lymph nodes (whether target/non-target) must have reduction in short axis to <10 mm.PR:at least a 30% decrease in sum of diameters of target lesions,taking as reference baseline sum diameters.PD:at least 20% increase in sum of diameters of target lesions,unequivocal progression of existing non-target lesions. Subset of ITT population who had an objective response. Here, '99999': values were not estimable due to insufficient number of participants with events at study termination.

End point type	Secondary

End point timeframe:

From the date of first response to the date of first documented tumor progression, death due to any cause or data cut-off date whichever comes first (maximum duration: 183 weeks)

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: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	3		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Plasma Concentration of Amcenestrant

End point title	Chinese Cohort: Plasma Concentration of Amcenestrant[23]

End point description:

Amcenestrant plasma concentrations at specified time points are reported. Analysis was performed on Pharmacokinetic-evaluable population: all participants who were assigned to study intervention, took at least 1 dose of study intervention, had at least 1 available plasma concentration post treatment with adequate documentation of date and time of dosing and date and time of sampling. Here, 'n' = participants with available data for each specified category. Data for this outcome measure was not planned to be collected and analyzed for PCEM group arm.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 1.5 hours(h), 4h post-dose, Cycle 1 Day 15: pre-dose; Cycle 2 Day 1: pre-dose, 1.5h, 4h, 8h post-dose; Cycles 3, 4, and 6 Day 1: pre-dose

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: Data for this endpoint was not planned to be collected and analyzed for PCEM arm.

End point values	Amcenestrant-Chinese Cohort			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1: 1.5h (n = 35)	3643.3 (± 3166.2)			
Cycle 1 Day 1: 4h (n = 46)	6015.0 (± 2887.0)			
Cycle 1 Day 15: Pre-dose (n = 31)	694.3 (± 589.4)			
Cycle 2 Day 1: Pre-dose (n = 43)	553.2 (± 316.9)			
Cycle 2 Day 1: 1.5h (n = 30)	3318.1 (± 3097.9)			
Cycle 2 Day 1: 4h (n = 31)	4912.9 (± 2513.9)			
Cycle 2 Day 1: 8h (n = 30)	3309.7 (± 1318.7)			
Cycle 3 Day 1: Pre-dose (n = 37)	521.6 (± 439.9)			
Cycle 4 Day 1: Pre-dose (n = 30)	475.1 (± 301.2)			
Cycle 6 Day 1: Pre-dose (n = 16)	598.5 (± 379.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Change From Baseline in European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire Domain Scores

End point title	Chinese Cohort: Change From Baseline in European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire Domain Scores[24]

End point description:

EORTC-QLQ-C30:cancer-specific instrument with 30 questions for evaluation of new chemotherapy & assessment of participant reported outcome.These include 5 functional scales, 9 symptom scales, &

GHS/QoL. All 14 items/domains were scored on scale of 1 (not at all) to 4 (very much) and GHS/QoL, scored on scale of 1 (very poor) to 7 (excellent). All scales are transformed from raw scores to linear scales ranging 0 to 100. Higher score for functional & GHS/QoL = higher level of functioning, & higher score for symptoms scales = higher symptom burden. LS mean and SE are derived from MMRM model with change from baseline values as response variable, treatment, time, treatment-by-time interaction, Baseline value and stratifications factors as fixed effect. Average of LS mean change from baseline values of overall treatment (i.e., each cycle [Cycles 2, 3, 4 and 6]) was reported. Safety population. Here, 'n' = participants with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, overall treatment duration (Cycles 2, 3, 4 and 6 [i.e., 183 weeks])

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	39		
Units: score on a scale				
least squares mean (standard error)				
GHS/QoL (n = 35, 38)	6.4 (± 2.6)	0.3 (± 2.5)		
Physical functioning (n = 35, 39)	4.3 (± 1.4)	0.9 (± 1.3)		
Role functioning (n = 35, 39)	-1.9 (± 2.5)	-0.1 (± 2.4)		
Emotional functioning (n = 35, 39)	-1.0 (± 2.0)	-1.7 (± 1.9)		
Cognitive functioning (n = 35, 39)	-0.4 (± 2.0)	-2.5 (± 1.9)		
Social functioning (n = 35, 39)	3.0 (± 2.3)	-1.9 (± 2.2)		
Fatigue (n = 35, 39)	-1.4 (± 2.1)	0.8 (± 2.0)		
Nausea and vomiting (n = 35, 39)	-0.9 (± 1.9)	0.9 (± 1.8)		
Pain (n = 35, 39)	-2.1 (± 2.1)	-2.3 (± 2.0)		
Dyspnoea (n = 35, 39)	-0.3 (± 2.5)	2.3 (± 2.4)		
Insomnia (n = 35, 39)	-0.9 (± 2.5)	-1.4 (± 2.4)		
Appetite loss (n = 35, 39)	-1.9 (± 2.7)	2.3 (± 2.6)		
Constipation (n = 35, 39)	2.3 (± 2.1)	2.8 (± 2.0)		
Diarrhoea (n = 35, 39)	-0.7 (± 1.1)	-0.2 (± 1.1)		
Financial difficulties (n = 35, 38)	-7.3 (± 3.3)	-6.4 (± 3.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels Score: Visual Analog Scale Score

End point title	Chinese Cohort: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels Score: Visual Analog Scale Score[25]

End point description:

EQ-5D-5L is a standardized measure of health status, provides a simple, generic measure of health for clinical and economic appraisal, and consists of 2 sections: the EQ-5D-5L health state utility index (descriptive system) and the EQ-5D-5L VAS. The Visual Analogue Scale is designed to rate the participant's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. LS mean and SE are derived from MMRM model with change from baseline values as response variable, treatment, time, treatment-by-time interaction, Baseline value and stratifications factors as fixed effect. Average of LS mean change from baseline values of overall treatment (i.e., each cycle [Cycles 2, 3, 4 and 6]) was reported in this outcome measure. Analysis was performed on Safety population evaluable. Here, "number of subjects analyzed" signifies participants with available data for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, overall treatment duration (Cycles 2, 3, 4 and 6 [i.e.,183 weeks])

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: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	39		
Units: score on a scale				
least squares mean (standard error)	3.6 (± 1.3)	1.2 (± 1.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels Score: Health Utility Index Value

End point title	Chinese Cohort: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels Score: Health Utility Index Value[26]

End point description:

EQ-5D-5L:consists of 2 sections:EQ-5D-5L health state utility index(descriptive system) & VAS.EQ-5D descriptive system consists of 5 dimensions:mobility,self-care,usual activities, pain/discomfort & anxiety/depression.Each dimension has 5 levels:no problems,slight problems,moderate problems,severe problems,& extreme problems.Response options are measured with 5-point Likert scale(for 5L version).EQ-5D-5L responses are converted into single index utility score between 0 to 1,higher score:better health state & lower score:worse health state. LS mean and SE are derived from MMRM model with change from baseline values as response variable,treatment, time,treatment-by-time interaction, Baseline value and stratifications factors as fixed effect. Average of LS mean change from baseline values overall treatment (i.e., each cycle [Cycles 2, 3, 4 and 6]) was reported.Safety population evaluable. 'Number of subjects analyzed'=participants with available data for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, overall treatment duration (Cycles 2, 3, 4 and 6 [i.e.,183 weeks])

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: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	40		
Units: score on a scale				
least squares mean (standard error)	-0.0 (± 0.0)	0.0 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chinese Cohort: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Breast Cancer Specific Module Domain Scores

End point title	Chinese Cohort: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Breast Cancer Specific Module Domain Scores[27]

End point description:

QLQ-BR23:disease-specific Health-related QOL.EORTC-QLQ-BR23 had 23 items:multi-item scales & single-item measures.4 functional scales(body image,sexual functioning,sexual enjoyment,future perspective) & 4 scales related to symptoms of disease or treatment(arm symptoms,breast symptoms,systemic therapy side effects,& upset by hair loss).All items scored 1(not at all) to 4(very much).Scores of all scales transformed from raw scores to linear scales,range:0 to 100.Higher score(functional):better outcome;higher score(symptoms):higher symptom burden.LS mean & SE derived from MMRM model with change from baseline values as response variable,treatment,time,treatment-by-time interaction,Baseline value & stratifications factors as fixed effect.Average of LS mean change from baseline values of overall treatment(each cycle[Cycles 2,3,4 & 6]).'Number of subjects analyzed': participants with available data for this outcome measure.Only items with atleast 10 participants by treatment group included.

End point type	Secondary

End point timeframe:

Baseline, overall treatment duration (Cycles 2, 3, 4 and 6 [i.e.,183 weeks])

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was evaluated for Chinese cohort only.

End point values	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	40		
Units: score on a scale				

least squares mean (standard error)				
Body image	-0.8 (± 2.4)	0.2 (± 2.3)		
Sexual functioning	-1.6 (± 1.3)	-3.6 (± 1.3)		
Future perspective	8.3 (± 3.2)	5.1 (± 3.0)		
Systemic therapy side effects	-0.5 (± 1.1)	0.5 (± 1.0)		
Breast symptoms	0.8 (± 1.7)	0.5 (± 1.6)		
Arm symptoms	-0.4 (± 1.4)	-0.8 (± 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Main Cohort and Chinese Cohort: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Main Cohort and Chinese Cohort: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. An SAE was defined as any untoward medical occurrence that, at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability/incapacity, was a congenital anomaly/birth defect or was a medically important event. TEAEs were defined as AEs that developed, worsened (according to the Investigator's opinion), or became serious during the on-treatment period. Analysis was performed on Safety population evaluable.

End point type	Secondary

End point timeframe:

From first dose of study treatment (Cycle 1 Day 1) up to 152 weeks for main cohort and 183 weeks for Chinese cohort

End point values	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant-Main Cohort	Physician Choice Endocrine Monotherapy (PCEM)-Chinese Cohort	Amcenestrant-Chinese Cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	147	143	42	48
Units: participants				
Any TEAE	113	118	22	33
Any TESAE	16	25	2	5

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs: From first dose of study treatment (Cycle 1 Day 1) up to 152 weeks (main cohort) and 183 weeks (Chinese cohort). Deaths: First dose of study drug (Day 1) to the end of follow-up for death for each participant, up to approximately 761 days

Adverse event reporting additional description:

Analysis was performed on Safety population evaluable.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort

Reporting group description:

Participants received potential control treatment of the choice of the physician depending on each participant’s medical condition and in accordance with the approved label. Control treatment included one of the following treatments to be selected before randomization and used as monotherapy: 1) Fulvestrant 500 mg, given as two 5-mL IM injections on Cycle 1 Days 1 and 15, and at Day 1 of each 28-day treatment cycle thereafter; or 2) Aromatase inhibitors (anastrozole 1 mg or letrozole 2.5 mg or exemestane 25 mg) PO, QD; or 3) Tamoxifen 20 mg/day PO, QD or twice a day (maximum exposure: 116 weeks).

Reporting group title	Amcenestrant- Chinese Cohort

Reporting group description:

Participants received 4 capsules of 100 mg, amcenestrant PO, QD from Day 1 to Day 28 in each 28-day treatment cycle until precluded by unacceptable toxicity or disease progression or participant's request to stop treatment or Investigator decision, whichever occurred first (maximum treatment exposure: 183 weeks).

Reporting group title	Physician Choice Endocrine Monotherapy (PCEM)- Chinese Cohort

Reporting group description:

Participants received potential control treatment of the choice of the physician depending on each participant's medical condition and in accordance with the approved label. Control treatment included one of the following treatments to be selected before randomization and used as monotherapy: 1) Fulvestrant 500 mg, given as two 5-mL IM injections on Cycle 1 Days 1 and 15, and at Day 1 of each 28-day treatment cycle thereafter; or 2) Aromatase inhibitors (anastrozole 1 mg or letrozole 2.5 mg or exemestane 25 mg) PO, QD; or 3) Tamoxifen 20 mg/day PO, QD or twice a day (maximum treatment exposure: 183 weeks).

Reporting group title	Amcenestrant- Main Cohort

Reporting group description:

Participants received 4 capsules of 100 mg, amcenestrant PO, QD from Day 1 to Day 28 in each 28-day treatment cycle until precluded by unacceptable toxicity or disease progression or participant’s request to stop treatment or Investigator decision, whichever occurred first (maximum exposure: 116 weeks).

Serious adverse events	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant- Chinese Cohort	Physician Choice Endocrine Monotherapy (PCEM)- Chinese Cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 147 (10.88%)	5 / 48 (10.42%)	2 / 42 (4.76%)
number of deaths (all causes)	52	6	2
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	0 / 147 (0.00%)	1 / 48 (2.08%)	0 / 42 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 147 (0.00%)	1 / 48 (2.08%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Pyrexia			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Peripheral Swelling			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Disease Progression			
subjects affected / exposed	2 / 147 (1.36%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 147 (0.00%)	1 / 48 (2.08%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Immune system disorders			
Contrast Media Allergy			

subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast Pain			
subjects affected / exposed	0 / 147 (0.00%)	1 / 48 (2.08%)	0 / 42 (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			
Cough			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	4 / 147 (2.72%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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	0 / 147 (0.00%)	1 / 48 (2.08%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 48 (2.08%)	0 / 42 (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

Psychiatric disorders			
Confusional State			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Investigations			
Blood Bilirubin Increased			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Postoperative Respiratory Distress			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Fractures			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Rib Fracture			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			

subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Cardiac Failure			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Transient Ischaemic Attack			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Migraine			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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

Ascites			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Haemorrhage			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Gastritis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Nausea			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Pancreatitis Acute			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bone Pain			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Pathological Fracture			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Pain In Extremity			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19			
subjects affected / exposed	3 / 147 (2.04%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	2 / 147 (1.36%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
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 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peritonitis Bacterial			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
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 Abscess			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased Appetite			
subjects affected / exposed	0 / 147 (0.00%)	0 / 48 (0.00%)	0 / 42 (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

Serious adverse events	Amcenestrant- Main Cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 143 (17.48%)		
number of deaths (all causes)	46		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest Pain				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral Swelling				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disease Progression				
subjects affected / exposed	5 / 143 (3.50%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 5			
Death				
subjects affected / exposed	0 / 143 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Contrast Media Allergy				
subjects affected / exposed	0 / 143 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Breast Pain				

subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant Pleural Effusion			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural Effusion			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Investigations			
Blood Bilirubin Increased			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative Respiratory Distress			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple Fractures			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib Fracture			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial Fibrillation			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure			

subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Transient Ischaemic Attack			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastric Haemorrhage				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis Acute				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back Pain				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone Pain				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Pathological Fracture				
subjects affected / exposed	3 / 143 (2.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pain In Extremity				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral Disc Protrusion				
subjects affected / exposed	1 / 143 (0.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	0 / 143 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Covid-19				
subjects affected / exposed	0 / 143 (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 / 143 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis Acute				
subjects affected / exposed	0 / 143 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 143 (1.40%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peritonitis Bacterial				

subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast Abscess			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Decreased Appetite			
subjects affected / exposed	1 / 143 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Physician Choice Endocrine Monotherapy (PCEM)- Main Cohort	Amcenestrant-Chinese Cohort	Physician Choice Endocrine Monotherapy (PCEM)- Chinese Cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 147 (53.74%)	25 / 48 (52.08%)	14 / 42 (33.33%)
Vascular disorders			
Hot Flush			
subjects affected / exposed	13 / 147 (8.84%)	1 / 48 (2.08%)	0 / 42 (0.00%)
occurrences (all)	13	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 147 (10.20%)	3 / 48 (6.25%)	1 / 42 (2.38%)
occurrences (all)	16	3	1
General disorders and administration site conditions			
Injection Site Pain			

subjects affected / exposed	10 / 147 (6.80%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences (all)	21	0	0
Fatigue			
subjects affected / exposed	17 / 147 (11.56%)	4 / 48 (8.33%)	1 / 42 (2.38%)
occurrences (all)	18	4	1
Asthenia			
subjects affected / exposed	8 / 147 (5.44%)	1 / 48 (2.08%)	1 / 42 (2.38%)
occurrences (all)	8	1	1
Pyrexia			
subjects affected / exposed	5 / 147 (3.40%)	3 / 48 (6.25%)	1 / 42 (2.38%)
occurrences (all)	5	3	2
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 147 (7.48%)	5 / 48 (10.42%)	4 / 42 (9.52%)
occurrences (all)	11	7	4
Nausea			
subjects affected / exposed	13 / 147 (8.84%)	3 / 48 (6.25%)	1 / 42 (2.38%)
occurrences (all)	14	3	1
Diarrhoea			
subjects affected / exposed	9 / 147 (6.12%)	1 / 48 (2.08%)	1 / 42 (2.38%)
occurrences (all)	10	1	2
Vomiting			
subjects affected / exposed	5 / 147 (3.40%)	3 / 48 (6.25%)	1 / 42 (2.38%)
occurrences (all)	5	3	1
Abdominal Pain			
subjects affected / exposed	5 / 147 (3.40%)	0 / 48 (0.00%)	0 / 42 (0.00%)
occurrences (all)	5	0	0
Abdominal Pain Upper			
subjects affected / exposed	1 / 147 (0.68%)	1 / 48 (2.08%)	0 / 42 (0.00%)
occurrences (all)	1	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 147 (5.44%)	6 / 48 (12.50%)	6 / 42 (14.29%)
occurrences (all)	8	6	7
Dyspnoea			

subjects affected / exposed	11 / 147 (7.48%)	2 / 48 (4.17%)	1 / 42 (2.38%)
occurrences (all)	11	2	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 147 (2.72%)	1 / 48 (2.08%)	1 / 42 (2.38%)
occurrences (all)	4	1	1
Musculoskeletal and connective tissue disorders			
Pain In Extremity			
subjects affected / exposed	10 / 147 (6.80%)	2 / 48 (4.17%)	0 / 42 (0.00%)
occurrences (all)	10	2	0
Back Pain			
subjects affected / exposed	17 / 147 (11.56%)	1 / 48 (2.08%)	2 / 42 (4.76%)
occurrences (all)	19	1	3
Arthralgia			
subjects affected / exposed	14 / 147 (9.52%)	2 / 48 (4.17%)	0 / 42 (0.00%)
occurrences (all)	14	2	0
Infections and infestations			
Covid-19			
subjects affected / exposed	3 / 147 (2.04%)	3 / 48 (6.25%)	2 / 42 (4.76%)
occurrences (all)	3	3	2
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	7 / 147 (4.76%)	2 / 48 (4.17%)	1 / 42 (2.38%)
occurrences (all)	7	2	1
Hypocalcaemia			
subjects affected / exposed	0 / 147 (0.00%)	3 / 48 (6.25%)	1 / 42 (2.38%)
occurrences (all)	0	6	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 147 (0.00%)	3 / 48 (6.25%)	0 / 42 (0.00%)
occurrences (all)	0	6	0

Non-serious adverse events	Amcenestrant- Main Cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 143 (60.14%)		
Vascular disorders			
Hot Flush			

subjects affected / exposed	13 / 143 (9.09%)		
occurrences (all)	13		
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 143 (12.59%)		
occurrences (all)	19		
General disorders and administration site conditions			
Injection Site Pain			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	16 / 143 (11.19%)		
occurrences (all)	18		
Asthenia			
subjects affected / exposed	11 / 143 (7.69%)		
occurrences (all)	16		
Pyrexia			
subjects affected / exposed	5 / 143 (3.50%)		
occurrences (all)	5		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 143 (4.90%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	28 / 143 (19.58%)		
occurrences (all)	36		
Diarrhoea			
subjects affected / exposed	14 / 143 (9.79%)		
occurrences (all)	20		
Vomiting			
subjects affected / exposed	27 / 143 (18.88%)		
occurrences (all)	43		
Abdominal Pain			
subjects affected / exposed	8 / 143 (5.59%)		
occurrences (all)	9		
Abdominal Pain Upper			

subjects affected / exposed	8 / 143 (5.59%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 143 (4.90%)		
occurrences (all)	7		
Dyspnoea			
subjects affected / exposed	7 / 143 (4.90%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	9 / 143 (6.29%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Pain In Extremity			
subjects affected / exposed	8 / 143 (5.59%)		
occurrences (all)	9		
Back Pain			
subjects affected / exposed	18 / 143 (12.59%)		
occurrences (all)	20		
Arthralgia			
subjects affected / exposed	18 / 143 (12.59%)		
occurrences (all)	22		
Infections and infestations			
Covid-19			
subjects affected / exposed	2 / 143 (1.40%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	10 / 143 (6.99%)		
occurrences (all)	11		
Hypocalcaemia			
subjects affected / exposed	0 / 143 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			

subjects affected / exposed occurrences (all)	0 / 143 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2019	Following Changes were made: Text in schema was updated as OS follow-up every 2 months until 18 months after PFS cut-off date; Updated tumor assessment schedule, bone scan schedule, tumor specimen/biopsy schedule; Cut-off date for the presentation of TED14856 results updated from 22 October 2018 to 29 May 2019; Amcenestrant benefit information updated to align with the updated Investigator's Brochure as number of participants with stable disease updated from 7 to 8; number of participants with long-term stable disease updated from 3 to 7; clinical benefit observed in 8 participants; Amcenestrant safety information updated as treatment-emergent adverse event results from TED14856 study Part A included; Remaining information removed and referred to the Investigator's Brochure; exploratory endpoint updated as to align with the updated schedule for ESR1 analysis and with the updated tumor specimen/biopsy schedule; Updated pharmacokinetic information related to Amcenestrant obtained from healthy volunteers and participants was included, updates to exclude participants with high thromboembolic risk; Clarified screen failures; Clarified dispensing and shipping procedures for IMP in case of direct to participant shipment of IMPs; Clarified recall procedures; Clarified dose modifications and management of amcenestrant toxicities; Clarified bone scan procedures when no lesions detected at screening; Clarified AE collection procedures; text updated to comply with the Sponsor standard procedures in Biomarker section; Clarified the statistical hypotheses; clarified the PFS censoring procedures; Clarified the DOR censoring procedures; clarified consenting procedures; Consistent updates made in appendices with the protocol amendment.
13 February 2020	Following Changes were made:Protocol title,short title updated;The NCT number included NCT04059484;Updated synopsis & schema for clarity,Screening assessment for follicle-stimulating hormone & estradiol assessment for premenopausal women was added; New assessments were added to the schedule of activities:Estradiol,Genetic sampling for drug metabolising enzymes & transporters (amcenestrant treatment arm only);Updated to include the most up to date information on potential amcenestrant risks anticipated in humans; Overall survival was relocated as the first secondary objective; Clarified that men were included in study; Updates made to align with possible dosing regimens for tamoxifen, as per label; COD projections updated following newly added futility interim analysis for PFS & inclusion of OS as key secondary endpoint; COD definitions updated for clarity;Recruitment period for Chinese population extended after sample size was revised for this population;Contraceptive guidance for male participants was included; participants with bone-only metastasis were allowed in this study; clarified to include all potential UGT inhibitors;Time window for amcenestrant dosing added; Updates that participants that were benefiting from the medication to continue treatment after a delay longer than 2 weeks;Clarified concomitant administration of strong and moderate CYP3A4 inducers and moderate CYP2C8 inducers was not to be permitted in participants receiving amcenestrant, since they may decrease amcenestrant exposure;Estradiol assessments included to explore the possible influence of circulating levels of estradiol on the efficacy of amcenestrant; A new section included for investigation of allelic variants of drug metabolising enzymes and/or drug transporters; clarified statistical hypotheses for the key secondary endpoint (OS);Sample size calculation updated in accordance with newly added futility interim analysis for PFS. Improvement in median PFS was corrected from 35 to 53%.

30 June 2020	Following changes were made: Introduced of study name AMEERA 3; Updates to allow some flexibility in the assessment of the vital signs following the first intake of the IMP; updates to specify Estradiol sampling at predose; Contingency measures for a regional or national emergency information added; potential risk related to amcenestrant added as risk of severe rash; tertiary/exploratory objective and endpoint have were updated to indicate that the biopsies were optional; updates to clarify the scope of Data Monitoring Committee (DMC) responsibility - as the interim analyses on Overall Survival will happen at the time of final Progression Free Survival, treatment would be unblinded and thus there was no need for DMC at that time; Updates to specify that the previous treatment with a CDK 4/6 inhibitor and the limitation to the number of participants naïve to CDK4/6 inhibitors does not apply to the participants of the extension study; Clarified and harmonised the definition of Human epidermal growth factor receptor (HER) non over-expressing tumors; Updates to mark biopsy procedures was categorised as optional; definition of secondary endocrine resistance updated; definition of a "sexually active male" clarified; duration of avoiding the natural or artificial sunlight exposure updated; the assessment of the estrogen receptor degradation with the biopsies, updated as optional; harmonised the wording of the samples' storage with the informed consent form.
17 December 2020	Following changes were made: The definitions of Disease Control Rate (DCR) and Clinical Benefit Rate (BCR) have been updated to add the "Non-Complete Response/Non-Progressive Disease" in the endpoint's descriptions; Texts updated to take in account that Estradiol levels can be high due to Fulvestrant intake; Added clarification on bone scans schedule; Risk of male infertility was added; Updated exclusion criteria with new data available on drug interactions (BCRP substrates, CYP3A and CYP2C8 inducers); Revised the futility analysis; to add risk minimisation strategies for pregnancy, osteoporosis induced by endocrine therapies, hepatic toxicity, and photosensitivity; Adverse events of special interests (AESI) section updated to provide guidance in case of an ALT increase; deleted a section which could be misunderstood in the AEs/SAEs reporting process; Clarification added on PROs schedule, to take in account that end of treatment (EOT) visit can be performed before 30 days following last IMP (if further therapy is started); Text added to allow remote-monitoring when allowed by local regulations, if on-site monitoring is not possible; Clarified that renal function calculation needed on top of the creatinine level for all participants; Updates in collection of pregnancy information; List of CYP sensitive substrates were updated; Added a copy of the following PROs English-language questionnaires: EORTC QLQ-C30, EORTC BR-23 (for female and male participants) and EQ-5D-5L.
23 September 2021	Following changes were made: Updates to clarify that after COD for final PFS analysis, data collected would be limited to exposure data, reason of EOT, and safety events and its related information when adverse event is serious or related to IMP; For planned cutoff date (previously database lock date) for the Chinese participants, sentence removed i.e., approximately 18 months after the PFS analysis of the global study; Exclusion criterion was adjusted to remove sensitive substrates of P-gp and BCRP and add sensitive substrates of OATP1B1/B3. And a note was added under this exclusion criteria to refer to FDA website; Sensitive substrates of P-gp and BCRP related information was removed, sensitive substrates of OATP1B1/B3 related information added to concomitant therapy section; Text removed to update caution to be taken with the proton pump inhibitors; Clarified the responsibilities for the monitoring, as a commitment to Belgium Health Authority requirement; Clarified that only amcenestrant is in scope of this 'recommended dose modification' table; Updated the required PK samples of the "full-PK" population in China, when sampling is difficult for participants; Clarified that specificities regarding exploratory endpoints in China per local regulations apply also for participants from China enrolled in the global part of the study; Clarified the sample size determination section, and to clarify the current definition of the COD rule for the Chinese population; Clarified that participants who agree to have samples taken for the full PK assessments were required to sign a separate section of the ICF rather than a separate ICF; Correction of typographical errors and minor inconsistencies across different sections, and clarifications were aligned with latest protocol template.
10 December 2021	Following updates were made: The definition of the COD for the final PFS and OS analysis was changed; The definition of the censoring and event scheme for the PFS analysis was changed; text added to clarify that SAEs are in scope of data to be collected post-COD, even if not related to IMP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early because it did not meet its primary objective of improved PFS with amcenestrant versus endocrine treatment of physician's choice.

Notes: