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	

Results information

Result version number	v1
This version publication date	15 April 2023
First version publication date	15 April 2023

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	Interim
Date of interim/final analysis	08 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 February 2022
Global end of trial reached?	No

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 subjects with metastatic or locally advanced breast cancer.

Protection of trial subjects:

Subjects 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 subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject 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: 13
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	Turkey: 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	290
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)	190
From 65 to 84 years	99
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 88 active centres in 22 countries. A total of 366 subjects were screened between 22 October 2019 and 15 April 2021 in the global cohort, of which 76 were screen failures. Screen failures were mainly due to not meeting eligibility criteria. Results reported based on primary completion date of 15 February 2022.

Pre-assignment

Screening details:

Randomisation stratified by presence of visceral metastasis (at least 1 liver/lung metastasis; yes/no), prior treatment with cyclin-dependent kinase(CDK)4/6 inhibitor; yes/no), Eastern Cooperative Oncology Group (ECOG) status (0/1). Assignment to arms was done in a 1:1 ratio using interaction response technology.

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?	Yes
Arm title	Physician Choice Endocrine Monotherapy (PCEM)

Arm description:

Subjects received potential control treatment of the choice of the physician depending on each subject's medical condition and in accordance with the approved label. Control treatment included one of the following treatments to be selected before randomisation and used as monotherapy: 1) Fulvestrant 500 mg, given as two 5 millilitres (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 daily (QD); or 3) Tamoxifen 20 milligrams per day (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	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.	
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	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.	
Arm title	Amcenestrant
Arm description: Subjects 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 subject'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.	

Number of subjects in period 1	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant
Started	147	143
Completed	0	0
Not completed	147	143
Consent withdrawn by subject	5	3
Adverse event, non-fatal	2	5
Ongoing	20	20
Unspecified	8	3
Progressive disease	112	112

Baseline characteristics

Reporting groups	
Reporting group title	Physician Choice Endocrine Monotherapy (PCEM)

Reporting group description:

Subjects received potential control treatment of the choice of the physician depending on each subject's medical condition and in accordance with the approved label. Control treatment included one of the following treatments to be selected before randomisation and used as monotherapy: 1) Fulvestrant 500 mg, given as two 5 millilitres (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 daily (QD); or 3) Tamoxifen 20 milligrams per day (mg/day) PO, QD or twice a day (maximum exposure: 116 weeks).

Reporting group title	Amcenestrant

Reporting group description:

Subjects 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 subject's request to stop treatment or Investigator decision, whichever occurred first (maximum exposure: 116 weeks).

Reporting group values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant	Total
Number of subjects	147	143	290
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.2	58.2	
standard deviation	± 12.5	± 11.8	-
Gender categorical Units: Subjects			
Female	146	143	289
Male	1	0	1
Race Units: Subjects			
White	102	102	204
Black or African American	0	0	0
Asian	34	32	66
Native Hawaiian or other Pacific Islander	2	0	2
American Indian or Alaska Native	0	0	0
Multiple	2	0	2
Unknown or Not reported	7	9	16

End points

End points reporting groups

Reporting group title	Physician Choice Endocrine Monotherapy (PCEM)

Reporting group description:

Subjects received potential control treatment of the choice of the physician depending on each subject's medical condition and in accordance with the approved label. Control treatment included one of the following treatments to be selected before randomisation and used as monotherapy: 1) Fulvestrant 500 mg, given as two 5 millilitres (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 daily (QD); or 3) Tamoxifen 20 milligrams per day (mg/day) PO, QD or twice a day (maximum exposure: 116 weeks).

Reporting group title	Amcenestrant

Reporting group description:

Subjects 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 subject's request to stop treatment or Investigator decision, whichever occurred first (maximum exposure: 116 weeks).

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the time in months interval from the date of randomisation 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. 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. Analysis was performed by Kaplan-Meier method. Analysis was performed on the ITT population which consist of all subjects from the enrolled population (with a signed informed consent form) who have been allocated a randomisation number by the Interactive Response Technology (IRT).

End point type	Primary

End point timeframe:

From randomisation 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)

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
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 endpoints were reported and continued when previous endpoint was statistically significant at one-sided 2.5% for the primary and the first secondary endpoint.

Comparison groups	Physician Choice Endocrine Monotherapy (PCEM) v Amcenestrant
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6437 [1]
Method	Logrank
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:

[1] - 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 CDK4/6 inhibitors and ECOG according to IRT.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time interval from the date of randomisation 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 subject 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% confidence interval (CI) were not estimable due to the smaller number of subjects with events.

End point type	Secondary

End point timeframe:

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

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
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 Subjects With Objective Response

End point title	Percentage of Subjects With Objective Response

End point description:

Objective response was defined as percentage of subjects 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 normalisation of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<) 10 millimetres (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 randomisation 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)

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	143		
Units: percentage of subjects				
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: Percentage of Subjects With Disease Control

End point title	Percentage of Subjects With Disease Control

End point description:

Disease control: defined as percentage of subjects having a confirmed CR, PR, or stable disease (SD) or Non-CR/Non-PD as Best overall response (BOR) determined by ICR as per RECIST 1.1 from date of randomisation to date of end of treatment. As per RECIST 1.1, CR: disappearance of all target & non-target lesions & normalisation 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 smallest sum diameters. Non-CR/Non-PD: persistence of one or more non-target 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. ITT population.

End point type	Secondary

End point timeframe:

From randomisation 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)

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	143		
Units: percentage of subjects				
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: Percentage of Subjects With Clinical Benefit

End point title	Percentage of Subjects With Clinical Benefit

End point description:

Clinical Benefit was defined as percentage of subjects 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 randomisation to the date of end of treatment. As per RECIST 1.1, CR: disappearance of all target and non-target lesions and normalisation 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 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 the ITT population.

End point type	Secondary

End point timeframe:

From randomisation 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)

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	143		
Units: percentage of subjects				
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: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR: time 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 subjects with ongoing response at time of analysis, DOR was censored at date of last valid disease assessment not showing documented progression performed before initiation of new anticancer treatment, if any. Per RECIST 1.1, CR: disappearance of all target and non-target lesions and normalisation of tumor marker level. Any pathological lymph nodes (whether target/non-target) must have reduction in short axis to <10 mm. PR: at least 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. Analysed on subset of subjects who had objective response. Here, 99999=space filler which denotes median & 95% CI upper limit were not estimable due to less number of subjects with events.

End point type	Secondary

End point timeframe:

From randomisation 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)

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
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

End point description:

PFS: time (in months) from randomisation 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 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 droplet digital polymerase chain reaction (ddPCR), including their mutant frequency & concentration. PFS is reported based on ESR1 mutation status of subjects: wild type & mutants. ESR1: gene encoding estrogen receptor alpha. ESR1 mutant type breast cancer: disease where ESR1 gene had mutation (i.e., a type of error). ESR1 wild type breast cancer: disease where ESR1 gene was normal without mutation. Kaplan-Meier method. ITT population. Here, 'number of subjects analysed' & 'n' = subjects with available data for this endpoint & each specified category, respectively.

End point type	Secondary

End point timeframe:

From randomisation 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)

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
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: Pharmacokinetics: Plasma Concentrations of Amcenestrant

End point title	Pharmacokinetics: Plasma Concentrations of Amcenestrant[2]

End point description:

Amcenestrant plasma concentrations at specified time points are reported. Analysis was performed on pharmacokinetic-evaluable population: all subjects 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' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 1.5 hours(hr), 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:

[2] - 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 analysed for PCEM arm.

End point values	Amcenestrant			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: nanograms per millilitre (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: Steady State Ctrough of Amcenestrant

End point title	Steady State Ctrough of Amcenestrant[3]

End point description:

Within-subject 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 subject. Average (mean) of all calculated Ctrough values for all subjects 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 analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose on Cycle 1 Day 15; Cycle 2 Day 1; Cycle 3 Day 1; Cycle 4 Day 1; Cycle 6 Day 1

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was not planned to be collected and analysed for PCEM arm.

End point values	Amcenestrant			
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 Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30) Domain Scores

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

End point description:

Cancer-specific instrument with 30 questions for evaluation of new chemotherapy & assessment of subject reported outcomes, 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 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 & standard error (SE) are 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 (i.e., each cycle [Cycle 1 up to Cycle 30]). Safety population evaluable. 'n'=subjects 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])

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
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: 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

End point description:

EQ-5D-5L: standardised 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 subject's current health state on scale from 0 to 100, where 0 = worst imaginable health state & 100 = best imaginable health state. 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 (i.e., each cycle [Cycle 1 up to Cycle 30]) was reported. Safety population evaluable which includes subjects 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 analysed'=subjects 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])

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
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 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

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). The EQ-5D-5L scores 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 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 (i.e., each cycle [Cycle 1 up to Cycle 30]) was reported. Safety population evaluable. Here, 'number of subjects analysed'=subjects 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])

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
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 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

End point description:

QLQ-BR23: disease-specific Health-related QOL assesses impact of breast cancer & side effects of treatment. EORTCQLQ-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. All items scored on 4-point scales; 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 for functional scales=better outcome; higher score for symptoms scales=higher symptom burden. LS mean & SE are 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 (i.e., each cycle [Cycle 1 up to 30]) was reported. Safety population evaluable. 'n' = subjects 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])

End point values	Physician Choice Endocrine Monotherapy (PCEM)	Amcenestrant		
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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE data was collected from Baseline up to 30 days after the last treatment administration (up to a maximum of 116 weeks), deaths were collected from Baseline up to the cut-off date (15 February 2022).

Adverse event reporting additional description:

Reported AEs are TEAEs that developed, worsened, or became serious during treatment period (first dose up to 30 days after last dose). Serious & Other AE collected for safety population only. Death all-cause data collected during study assessed for all randomised subjects. Disease progression related death were not reported as AE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Physician choice endocrine monotherapy (PCEM)

Reporting group description:

Subjects received potential control treatment of the choice of the physician depending on each subject's medical condition and in accordance with the approved label. Control treatment included one of the following treatments to be selected before randomisation 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 treatment 28-day 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 400 mg

Reporting group description:

Subjects 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 subject's request to stop treatment or Investigator decision, whichever occurred first (maximum exposure: 116 weeks).

Serious adverse events	Physician choice endocrine monotherapy (PCEM)	Amcenestrant 400 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 147 (10.20%)	23 / 143 (16.08%)	
number of deaths (all causes)	47	42	
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest Pain			

subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease Progression			
subjects affected / exposed	2 / 147 (1.36%)	4 / 143 (2.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 4	
Peripheral Swelling			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Contrast Media Allergy			
subjects affected / exposed	1 / 147 (0.68%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast Pain			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 147 (0.68%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	4 / 147 (2.72%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Bilirubin Increased			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Fractures			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Respiratory Distress			
subjects affected / exposed	1 / 147 (0.68%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Pectoris			

subjects affected / exposed	1 / 147 (0.68%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Migraine			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 147 (0.68%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 147 (0.68%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastric Haemorrhage			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 147 (0.68%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Extremity			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	0 / 147 (0.00%)	3 / 143 (2.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	3 / 147 (2.04%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonitis Bacterial			
subjects affected / exposed	1 / 147 (0.68%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 147 (0.68%)	2 / 143 (1.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	1 / 147 (0.68%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			

subjects affected / exposed	2 / 147 (1.36%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 147 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Physician choice endocrine monotherapy (PCEM)	Amcenestrant 400 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 147 (51.70%)	84 / 143 (58.74%)	
Vascular disorders			
Hot Flush			
subjects affected / exposed	13 / 147 (8.84%)	13 / 143 (9.09%)	
occurrences (all)	13	13	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 147 (9.52%)	18 / 143 (12.59%)	
occurrences (all)	14	19	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 147 (5.44%)	11 / 143 (7.69%)	
occurrences (all)	8	16	
Fatigue			
subjects affected / exposed	17 / 147 (11.56%)	16 / 143 (11.19%)	
occurrences (all)	18	18	
Injection Site Pain			

subjects affected / exposed	10 / 147 (6.80%)	0 / 143 (0.00%)	
occurrences (all)	20	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 147 (7.48%)	7 / 143 (4.90%)	
occurrences (all)	11	9	
Diarrhoea			
subjects affected / exposed	9 / 147 (6.12%)	14 / 143 (9.79%)	
occurrences (all)	10	17	
Nausea			
subjects affected / exposed	13 / 147 (8.84%)	28 / 143 (19.58%)	
occurrences (all)	14	34	
Vomiting			
subjects affected / exposed	5 / 147 (3.40%)	27 / 143 (18.88%)	
occurrences (all)	5	43	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 147 (5.44%)	6 / 143 (4.20%)	
occurrences (all)	8	6	
Dyspnoea			
subjects affected / exposed	11 / 147 (7.48%)	7 / 143 (4.90%)	
occurrences (all)	11	8	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 147 (2.04%)	9 / 143 (6.29%)	
occurrences (all)	3	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 147 (9.52%)	20 / 143 (13.99%)	
occurrences (all)	14	24	
Back Pain			
subjects affected / exposed	15 / 147 (10.20%)	18 / 143 (12.59%)	
occurrences (all)	17	20	
Pain In Extremity			
subjects affected / exposed	10 / 147 (6.80%)	8 / 143 (5.59%)	
occurrences (all)	10	9	

Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	 6 / 147 (4.08%) 6	 10 / 143 (6.99%) 11	

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 subjects with stable disease updated from 7 to 8; number of subjects with long-term stable disease updated from 3 to 7; clinical benefit observed in 8 subjects; 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 subjects was included, updates to exclude subjects with high thromboembolic risk; Clarified screen failures; Clarified dispensing and shipping procedures for IMP in case of direct to subject 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 & the 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 subjects was included; subjects with bone-only metastasis were allowed in this study; clarified to include all potential UGT inhibitors; Time window for amcenestrant dosing added; Updates that subjects 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 subjects 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 subjects naïve to CDK4/6 inhibitors does not apply to the subjects 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 subjects; 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 subjects) 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 subjects, 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 subjects; Clarified that specificities regarding exploratory endpoints in China per local regulations apply also for subjects 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 subjects 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

None reported