Clinical trial results:
Phase 2 Window Study of Two Dose Levels of Amcenestrant [SAR439859] (SERD) Versus Letrozole in Newly Diagnosed Pre-operative Post-menopausal Patients With ER Positive, HER2 Negative Primary Breast Cancer

Summary

EudraCT number	2019-002015-26
Trial protocol	FR ES BE IT
Global end of trial date	28 May 2021

Results information

Result version number	v1 (current)
This version publication date	12 June 2022
First version publication date	12 June 2022

Trial information

Trial identification

Sponsor protocol code	ACT16106

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04191382
WHO universal trial number (UTN)	U1111-1228-9473

Notes:

Sponsors

Sponsor organisation name	Sanofi Aventis Recherche & Développement
Sponsor organisation address	1 Avenue Pierre Brossolette, Chilly-Mazarin Cedex, 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	21 January 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 May 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether amcenestrant given at 2 different doses improved the antiproliferative activity when compared to letrozole.

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	04 February 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	United States: 13
Country: Number of subjects enrolled	Ukraine: 11
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Russian Federation: 15
Worldwide total number of subjects	105
EEA total number of subjects	57

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	64
From 65 to 84 years	39
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 32 active sites in 8 countries. A total of 135 subjects were screened from 04-February-2020 to 21-April-2021, of which 30 subjects were screen failures mainly due to selection criteria not met.

Pre-assignment

Screening details:

A total of 105 subjects with early breast cancer were randomised in 1:1:1 ratio to receive treatment with amcenestrant 400 milligrams (mg), amcenestrant 200 mg, or letrozole 2.5 mg.

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	Amcenestrant 400 mg

Arm description:

Subjects received 4 capsules of 100 mg of amcenestrant once daily (QD) from Day 1 to Day 14.

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

Dosage and administration details:

Amcenestrant 4 capsules of 100 mg administered orally.

Arm title	Amcenestrant 200 mg

Arm description:

Subjects received 2 capsules of 100 mg of amcenestrant QD from Day 1 to Day 14.

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

Dosage and administration details:

Amcenestrant 2 capsules of 100 mg administered orally.

Arm title	Letrozole 2.5 mg

Arm description:

Subjects received 2.5 mg of letrozole tablet QD from Day 1 to Day 14.

Arm type	Active comparator
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Letrozole 2.5 mg tablet administered orally.

Number of subjects in period 1	Amcenestrant 400 mg	Amcenestrant 200 mg	Letrozole 2.5 mg
Started	34	36	35
Treated	33	36	35
Completed	33	36	35
Not completed	1	0	0
Withdrawal by subject	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Amcenestrant 400 mg
Reporting group description:	
Subjects received 4 capsules of 100 mg of amcenestrant once daily (QD) from Day 1 to Day 14.	
Reporting group title	Amcenestrant 200 mg
Reporting group description:	
Subjects received 2 capsules of 100 mg of amcenestrant QD from Day 1 to Day 14.	
Reporting group title	Letrozole 2.5 mg
Reporting group description:	
Subjects received 2.5 mg of letrozole tablet QD from Day 1 to Day 14.	

Reporting group values	Amcenestrant 400 mg	Amcenestrant 200 mg	Letrozole 2.5 mg
Number of subjects	34	36	35
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.4	63.4	63.7
standard deviation	± 8.6	± 8.4	± 8.5
Gender categorical Units: Subjects			
Female	34	36	35
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	3	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	0
White	23	24	25
More than one race	0	1	1
Unknown or Not Reported	8	8	4
Ki67 expression at Baseline (n=32,36,32)			
Tumor tissue collected through a core-cut biopsy at Baseline was used to determine Ki67 expression. Ki67 expression was defined as the percentage of positive tumor cells assessed by central reading. Here, 'n' signifies subjects with available data at Baseline for the specified Baseline measure.			
Units: percentage of positive tumor cells			
arithmetic mean	33.8	31.2	32.6
standard deviation	± 16.3	± 14.3	± 18.5

Reporting group values	Total		
Number of subjects	105		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	105		
Male	0		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	10		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	72		
More than one race	2		
Unknown or Not Reported	20		
Ki67 expression at Baseline (n=32,36,32)			
Tumor tissue collected through a core-cut biopsy at Baseline was used to determine Ki67 expression. Ki67 expression was defined as the percentage of positive tumor cells assessed by central reading. Here, 'n' signifies subjects with available data at Baseline for the specified Baseline measure.			
Units: percentage of positive tumor cells arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Amcenestrant 400 mg
Reporting group description:	
Subjects received 4 capsules of 100 mg of amcenestrant once daily (QD) from Day 1 to Day 14.	
Reporting group title	Amcenestrant 200 mg
Reporting group description:	
Subjects received 2 capsules of 100 mg of amcenestrant QD from Day 1 to Day 14.	
Reporting group title	Letrozole 2.5 mg
Reporting group description:	
Subjects received 2.5 mg of letrozole tablet QD from Day 1 to Day 14.	

Primary: Percent Change From Baseline in Ki67 Level at Day 15

End point title	Percent Change From Baseline in Ki67 Level at Day 15

End point description:

Tumor tissue collected through a core-cut biopsy at Baseline and Day 15 was used to determine Ki67 expression. Ki67 expression was defined as the percentage of positive tumor cells assessed by central reading. Ki67 percent change from Baseline for a given subject was defined as 100*(Ki67pre - Ki67post)/Ki67pre, where Ki67pre and Ki67post were pre-treatment and post-treatment Ki67 value of the subject. Adjusted geometric least square (LS) means and 95% CI for percent change were obtained from analysis of covariance (ANCOVA) model of log proportional change i.e., log (Ki67post/ki67pre) with treatment and log-Ki67pre as fixed effect and converted by antilog transformation. Analysis was performed on modified intent-to-treat (mITT) population that included all enrolled subjects for whom there was confirmation of successful allocation of a randomisation number by IRT, who had taken at least one study drug, and who had both Baseline and post treatment available biopsies with Ki67 values.

End point type	Primary

End point timeframe:

Baseline, Day 15

End point values	Amcenestrant 400 mg	Amcenestrant 200 mg	Letrozole 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	35	29	
Units: percent change				
least squares mean (confidence interval 95%)	75.9 (67.9 to 81.9)	68.2 (58.4 to 75.7)	77.7 (70.0 to 83.4)	

Statistical analyses

Statistical analysis title	Amcenestrant 400 mg versus Letrozole 2.5 mg

Statistical analysis description:

Geometric LS-means ratio of proportional change was the ratio of geometric LS-means of the proportional change between groups (Amcenestrant 400 mg versus Letrozole 2.5 mg).

Comparison groups	Amcenestrant 400 mg v Letrozole 2.5 mg

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Ratio of Geometric Means
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.63

Notes:

[1] - Other descriptive analysis

Statistical analysis title	Amcenestrant 200 mg versus Letrozole 2.5 mg

Statistical analysis description:

Geometric LS-means ratio of proportional change was the ratio of geometric LS-means of the proportional change between groups (Amcenestrant 200 mg versus Letrozole 2.5 mg).

Comparison groups	Amcenestrant 200 mg v Letrozole 2.5 mg
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Ratio of Geometric Means
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	2.12

Notes:

[2] - Other descriptive analysis

Secondary: Proportion of Subjects With Percent Change From Baseline in Ki67 greater than or equal to (>=) 50 Percent at Day 15

End point title	Proportion of Subjects With Percent Change From Baseline in Ki67 greater than or equal to (>=) 50 Percent at Day 15

End point description:

Tumor tissue collected through a core-cut biopsy at Baseline and Day 15 was used to determine Ki67 expression. Ki67 expression was defined as the percentage of positive tumor cells assessed by central reading. Ki67 percent change from Baseline for a given subject was defined as 100*(Ki67pre - Ki67post) / Ki67pre, where Ki67pre and Ki67post were pre-treatment and post-treatment Ki67 value of the subject. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	Amcenestrant 400 mg	Amcenestrant 200 mg	Letrozole 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	35	29	
Units: proportion of subjects				
number (confidence interval 95%)	74.2 (55.4 to 88.1)	68.6 (50.7 to 83.1)	89.7 (72.6 to 97.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Estrogen Receptor (ER) Expression as Measured by H-Score at Day 15

End point title	Change From Baseline in Estrogen Receptor (ER) Expression as Measured by H-Score at Day 15

End point description:

Change from Baseline in ER expression was measured by H-Score. The H-score was calculated as the sum of the percent of cells staining positive (0 to 100) multiplied staining intensity level from 0 to 3 (0=none, 1=low, 2=moderate, 3=high). Total ER expression H-score ranged from 0 to 300, where higher score indicated stronger ER expression. Change from Baseline in H-Score equals H-scorepost minus H-scorepre; where H-scorepost and H-scorepre denoted post-treatment and pre-treatment H-scores, respectively. LS-means and 95% CI were obtained from an ANCOVA model for change from Baseline with treatment and Baseline as fixed effect. Analysis was performed on mITT population. Here, 'number of subjects analysed' signifies subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	Amcenestrant 400 mg	Amcenestrant 200 mg	Letrozole 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	32	28	
Units: score on a scale				
least squares mean (confidence interval 95%)	-176.7 (-201.4 to -152.0)	-202.9 (-226.1 to -179.7)	-32.5 (-57.2 to -7.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormalities: Haematological Parameters

End point title	Number of Subjects With Abnormalities: Haematological Parameters

End point description:

Haematology parameters covered by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) and included: Haemoglobin, Lymphocyte, Neutrophils, Leukocytes(white blood cells), Anaemia, Platelets, Eosinophils, and international normalised ratio (INR). NCI-CTCAE Grades 1-5 were described as: Grade1-Mild; asymptomatic/mild symptoms; Grade2-Moderate; minimal,

local or noninvasive intervention indicated; limiting age appropriate instrumental daily activities. Grade3-Severe/medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; Grade4-Life-threatening consequences; Grade5-Death. Data for 'All Grades' were reported in this endpoint. Safety population included all subjects who were randomly assigned to study drug and who took at least 1 dose of study drug. Here, 'subjects analysed'=subjects evaluable for this endpoint; 'n'=subjects with available data for specified categories for each arm.

End point type	Secondary

End point timeframe:

From first dose of study drug up to Day 14

End point values	Amcenestrant 400 mg	Amcenestrant 200 mg	Letrozole 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	35	35	
Units: Subjects				
White blood cell decreased (n=32,35,35)	5	6	3	
Neutrophil count decreased (n=32,35,35)	1	0	1	
Anaemia (hemoglobin decreased) (n=32,35,35)	6	4	1	
Haemoglobin increased (n=32,35,35)	0	0	0	
Platelet count decreased (n=32,35,35)	1	1	0	
Lymphocyte count decreased (n=32,35,35)	1	3	1	
INR increased (n=28,28,31)	0	0	0	
Eosinophilia (eosinophils increased) (n=32,35,35)	2	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormalities: Clinical Chemistry

End point title	Number of Subjects With Abnormalities: Clinical Chemistry

End point description:

Clinical chemistry laboratory parameters covered by NCI-CTCAE and included: Glucose, Potassium, Sodium, Creatinine. An NCI-CTCAE Grades 1 to 5 were described as: Grade 1-Mild; asymptomatic or mild symptoms; Grade 2-Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental daily activities; Grade 3-Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; Grade 4-Life-threatening consequences; Grade 5-Death. Data for 'All Grades' were reported in this endpoint. Analysis was performed on safety population. Here, 'number of subjects analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects with available data for specified categories for each arm, respectively.

End point type	Secondary

End point timeframe:

From first dose of study drug up to Day 14

End point values	Amcenestrant 400 mg	Amcenestrant 200 mg	Letrozole 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	35	35	
Units: Subjects				
Hypernatremia (sodium increased) (n=32,35,35)	1	1	1	
Hyponatremia (sodium increased) (n=32,35,35)	0	1	0	
Hyperkalemia (potassium increased) (n=32,35,35)	2	1	1	
Hypokalemia (potassium decreased) (n=32,35,35)	0	2	0	
Creatinine increased (n=32,34,35)	0	3	2	
Hypoglycemia (glucose decreased) (n=32,35,35)	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose up to 30 days following the last dose of study drug (up to 45 days)

Adverse event reporting additional description:

Reported adverse events (AEs) are treatment-emergent adverse events (TEAEs) i.e., AEs that developed, worsened, or became serious during the treatment period (time from the first dose of study drug up to 30 days after last dose of study drug). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Amcenestrant 400 mg

Reporting group description:

Subjects received 4 capsules of 100 mg of amcenestrant once daily (QD) from Day 1 to Day 14.

Reporting group title	Amcenestrant 200 mg

Reporting group description:

Subjects received 2 capsules of 100 mg of amcenestrant QD from Day 1 to Day 14.

Reporting group title	Letrozole 2.5 mg

Reporting group description:

Subjects received 2.5 mg of letrozole tablet QD from Day 1 to Day 14.

Serious adverse events	Amcenestrant 400 mg	Amcenestrant 200 mg	Letrozole 2.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	0 / 35 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Pneumonia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	0 / 35 (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
Wound Infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	0 / 35 (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

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

Non-serious adverse events	Amcenestrant 400 mg	Amcenestrant 200 mg	Letrozole 2.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 33 (33.33%)	12 / 36 (33.33%)	14 / 35 (40.00%)
Investigations			
Alanine Aminotransferase Increased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)	0 / 35 (0.00%)
occurrences (all)	1	2	0
Injury, poisoning and procedural complications			
Procedural Pain			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	2 / 35 (5.71%)
occurrences (all)	2	1	2
Vascular disorders			
Hot Flush			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	4 / 33 (12.12%)	1 / 36 (2.78%)	5 / 35 (14.29%)
occurrences (all)	4	1	5
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 33 (9.09%)	0 / 36 (0.00%)	2 / 35 (5.71%)
occurrences (all)	3	0	2
General disorders and administration site conditions			
Asthenia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 33 (6.06%)	2 / 36 (5.56%)	0 / 35 (0.00%)
occurrences (all)	2	2	0
Fatigue			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	1 / 35 (2.86%)
occurrences (all)	2	1	1
Feeling Cold			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Constipation			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Diarrhoea			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 33 (0.00%)	3 / 36 (8.33%)	3 / 35 (8.57%)
occurrences (all)	0	3	3
Reproductive system and breast disorders			
Breast Pain			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	3 / 35 (8.57%)
occurrences (all)	1	0	3
Psychiatric disorders			
Anxiety			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)	0 / 35 (0.00%)
occurrences (all)	1	2	0
Insomnia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	4 / 33 (12.12%)	1 / 36 (2.78%)	0 / 35 (0.00%)
occurrences (all)	4	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)	3 / 35 (8.57%)
occurrences (all)	2	0	3
Metabolism and nutrition disorders			

Decreased Appetite			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	0 / 35 (0.00%)
occurrences (all)	2	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2020	Following changes were made: •Added details on information for demography and added follicle stimulating hormone (FSH) test. •Added one blood sample for SAR439859 treatment arms to investigate allelic variants of drug metabolising enzymes and/or drug transporters. •Revised core-cut biopsy from surgery specimen. •For clinical sites reporting Ki67 expression by range rather than single value, local re-evaluation might be requested to confirm Ki67 expression >=15%.” was added. •Revised safety data language according to new approved version of investigator's brochure. •Modified inclusion criteria (IC) to add Stage I subjects and subjects intended for upfront mastectomy. •Modified IC to remove premenopausal women on gonadotropin releasing hormone analog and perimenopausal women (cessation of menses of duration less than or equal to [<=] 12 months). •Modified a breast tumor size of at least 10 millimetres (mm) in greatest dimension measured by ultrasound. •Modified exclusion criteria(EC) to recent use of hormone replacement therapy (last dose <=30 days prior to randomisation). •New EC added and drugs that were potential inhibitors of UDP-glucuronosyltransferases (UGTs) were moved to prohibited list. •The duration of sun protection for subjects taking SAR439859 was extended to during study treatment and for at least 5 days after discontinuation of SAR439859. •Dose modification criteria for SAR439859 and letrozole was modified to not allow any dose modification or reintroduction of study drug for NCI CTCAE Grade >=3 AEs. •Modified asymptomatic overdose had to be reported as a standard AE. •Diagnostic biopsy baseline sample timelines changed to within 4 weeks prior to randomisation. •The fixing time for the tumor biopsy sample was revised to 24-72 hours prior to processing and embedding at local pathology centres. •Genome-wide sequencing of DNA isolated to mutation analysis of DNA isolated from tumor biopsy. •Estradiol was removed from screening tests.

04 February 2021	Following changes were made: •Updated protocol to reflect serial FSH measurements were required to confirm postmenopausal status for subjects who had received hormonal replacement therapy but had discontinued treatment and in absence of amenorrhea >12 months. •Added Cyclin D1 in exploratory protein biomarker panel-tested by IHC in tumor tissues. •Added Complete Cell Cycle Arrest (CCCA) as exploratory endpoint to further assess impact on proliferation; and added digital assessment of protein biomarkers. •Removed PK sampling on Day 1, Day 7, and added sampling on Day 15. •Added "or country's legal age of majority if legal adult age was >18 years old". •Added hepatitis A/B/C viral serologies at screening. Updated to exclude subjects with known active hepatitis A/B/C, or hepatic cirrhosis. •Updated EC to remove treatment with moderate Cytochrome P450, family 3, subfamily A (CYP3A) inducers; updated list of CYP3A inducer. •Removed EC-'Treatment with strong or moderate Cytochrome P4502C8 (CYP2C8) inducers within 2 weeks before first study drug administration or 5 elimination half-lives whichever was longest and could not be replaced'. Removed prohibited concomitant therapies with regards to CYP2C8 inducers. •Added BCRP substrate in prohibited concomitant medication. •Added recommendation of using broad spectrum sunscreens filtering both UVA and UVB light exposure. •Prolonged duration of prior treatment to be recorded in eCRF to "from 30days prior to randomisation". •Added phototoxicity reaction in AESI. •Added guidance on increase in alanine transaminase >=Grade 2 management. •Added new section describing contingency measures for regional or national emergency that was declared by government agency. •Changed statistical model from t-test to analysis of covariance model. •Updated formula of eGFR calculation and provided linkage. •Added INN name amcenestrant.

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 recruitment discontinued early based on strategic sponsor decision that was not driven by any safety concerns. No inferential statistical analysis was performed due to early termination.

Notes: