Sponsor: Sanofi **Drug substance:** Amcenestrant	**Study Identifiers:** U1111-1244-1767; NCT05128773; EudraCT Number: 2021-000398-10 **Study code:** EFC16133/BIG 20-01/AFT-55/EORTC-2033

Title of the study:

A randomized, multicenter, double-blind, Phase 3 study of amcenestrant (SAR439859) versus tamoxifen for the treatment of patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative or positive, stage IIB-III breast cancer who have discontinued adjuvant aromatase inhibitor therapy due to treatment-related toxicity

Study centers:

This study was conducted at 2 centers that screened and randomized participants in Chile and China.

Study period:

Date first participant enrolled: 17/Feb/2022

Date last participant completed: 13/Oct/2022

Study Status: Terminated (Sponsor decision to prematurely stop the study, not linked to any safety concern)

Phase of development: Phase 3

Objectives:

Primary:

- To determine whether amcenestrant once a day (QD) improves the invasive breast cancer-free survival (IBCFS) when compared to tamoxifen QD in patients with early breast cancer as adjuvant treatment

Secondary:

Key secondary endpoints

- To determine whether amcenestrant once a day (QD) improves the invasive disease-free survival (IDFS) when compared to tamoxifen QD in patients with early breast cancer as adjuvant treatment

Other secondary endpoints

- To evaluate the distant recurrence-free survival (DRFS) in both treatment arms
- To evaluate the locoregional recurrences-free survival (LRRFS) in both treatment arms
- To evaluate the overall survival (OS) in both treatment arms
- To evaluate the breast cancer-specific survival (BCSS) in both treatment arms
- To evaluate patient-reported overall treatment-related side effect bother, treatment-related symptoms, and quality of life in both treatment arms
- To evaluate safety in both treatment arms
- To characterize the pharmacokinetics (PK) of amcenestrant

Methodology:

This was a prospective, randomized, international, multicenter, double-blind, double-dummy, Phase 3 study comparing the efficacy and evaluating the safety of amcenestrant *versus* tamoxifen.

The study had 3 main periods: screening, active treatment, and follow up.

Men, pre/peri-menopausal women (with GnRH analog approved for use in early breast cancer) and post-menopausal women with HR+ early breast cancer, who had discontinued adjuvant AI therapy due to treatment-related toxicity entered the screening period to assess their eligibility.

Participants still on AI treatment entered the screening period for central confirmation of biomarkers and screening imaging assessments. The other assessments/questionnaires required before randomization were performed/completed when patient was off the AI therapy.

All eligible participants, for whom ER and PgR status were centrally confirmed, were randomly assigned using an IRT to either amcenestrant 200 mg daily (experimental) arm or tamoxifen 20 mg daily (control) arm in a 1:1 ratio.

- Arm A: Amcenestrant 200 mg + tamoxifen-matching placebo
- Arm B: Amcenestrant-matching placebo + tamoxifen 20 mg

All randomized patients also received the matching placebo of the other treatment under evaluation. Both treatments were given orally.

The study population was stratified by the following factors, as reported at the time of randomization:

- Prior exposure to (neo)adjuvant AI therapy: ≤12 months vs. >12 months
- Prior exposure to (neo)adjuvant chemotherapy and HER2 status: HER2-negative breast cancer with NO prior (neo)adjuvant chemotherapy vs. HER2-negative breast cancer with prior (neo)adjuvant chemotherapy vs. HER2-positive breast cancer with prior (neo)adjuvant chemotherapy

Note: Participants with unknown HER2 status were classified as HER2-negative.

- Prior exposure to CDK4/6 inhibitor (Yes or No)
- Geographic regions (North America, Europe vs. Asia Pacific vs. Other)
- Men or peri-/pre-menopausal women vs. post-menopausal women

Number of participants: (planned and analyzed):

It was anticipated that approximately 4670 participants would be screened to achieve 3738 randomly assigned to study intervention with a balanced randomization ratio (1869 participants per intervention group).

A total of 6 participants were screened. Of the 6 participants, 3 were randomized and exposed to study treatment, amcenestrant. No participants were exposed to tamoxifen. The safety and intent-to-treat (ITT) population both contained 3 participants. All 3 participants did not complete the study period. The 3 participants discontinued due to the early termination of the trial by the Sponsor.

Diagnosis and criteria for inclusion:

This study included participants with high-risk Stage IIB-III estrogen receptor positive (ER[+]), PgR+ (≥10% positive stained cells), human epidermal growth factor receptor 2-negative or positive breast cancer who had discontinued adjuvant aromatase inhibitor therapy due to treatment-related toxicity. Prior aromatase inhibitor therapy must have been given for 6-30 months in duration prior to discontinuation.

Study products

Investigational medicinal product:

Amcenestrant (SAR439859) or amcenestrant (SAR439859)-matching placebo

- Amcenestrant formulation: 200 mg tablets
- Route of administration: oral route
- Dose regimen: the recommended dose was 200 mg once daily, to be taken approximately at the same time each day, with food.
- Amcenestrant-matching placebo was supplied as tablets identical to amcenestrant 200 mg tablets in appearance.

Tamoxifen or tamoxifen-matching placebo

- Tamoxifen formulation: 20 mg tablets
- Route of administration: oral route
- Dose regimen: the recommended dose was 20 mg once daily, to be taken approximately at the same time each day, with food.
- Tamoxifen-matching placebo was supplied as tablets identical to tamoxifen 20 mg tablets in appearance.

For IMPs, if a dose was vomited or omitted the participant should not take the dose later or 2 doses at the next planned dose.

Non investigational medicinal products:

Goserelin or other GnRH analog approved for use in early breast cancer as per site/country availability.

Duration of study intervention:

The planned duration of study intervention was 5 calendar years or until the occurrence of any withdrawal criterion, whichever occurs first.

Criteria for evaluation:

Primary:

IBCFS is defined according to Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP) criteria version 2.0 as the time interval from the date of randomization to the date of the first occurrence of one of the following events:

- Ipsilateral invasive breast tumor recurrence (IIBTR): invasive breast cancer involving the same breast parenchyma as the original primary.

- Local-Regional invasive breast cancer recurrence: invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.

- Distant recurrence: metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.

- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.

- Invasive Contralateral breast cancer.

Secondary:

Key secondary endpoints

- IDFS is defined according to STEEP criteria as the time interval from the date of randomization to the date of the first occurrence of one of the following events:
  - Ipsilateral invasive breast tumor recurrence (IIBTR): invasive breast cancer involving the same breast parenchyma as the original primary.
  - Local-Regional invasive breast cancer recurrence: invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.
  - Distant recurrence: metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
  - Death attributable to any cause, including breast cancer, nonbreast cancer, or unknown cause.
  - Invasive Contralateral breast cancer
  - Second nonbreast primary invasive cancer

Other secondary endpoints

- DRFS is defined according to STEEP criteria as the time interval from the date of randomization to the date of the first occurrence of one of the following events: distant recurrence or death attributable to any cause (including breast cancer, nonbreast cancer, or unknown cause)
- LRRFS is defined as the time interval from the date of randomization to the date of the first occurrence of one of the following events: local/regional ipsilateral recurrence, invasive contralateral breast cancer or death attributable to any cause (including breast cancer, nonbreast cancer, or unknown cause)
- OS is defined as the time interval from the date of randomization to the date of death due to any cause
- BCSS is defined as the time interval from the date of randomization to the date of death attributable to breast cancer cause
- This patient reported outcome (PRO) objective will be evaluated using the following endpoints:
  - Change from baseline in overall side effect bother as measured by the Functional Assessment of Cancer Therapy Item GP-5 (FACT-GP5)
  - Change from baseline in systemic therapy side effects as measured by the EORTC Quality of Life Questionnaire Breast cancer module (EORTC-QLQ-BR23) systemic therapy side effects scale

- Change from baseline in global health status/quality of life as measured by the EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30) global health status/quality of life (GHQ) scale

- Adverse events (AEs)/serious adverse events (SAEs), laboratory abnormalities and adverse events of special interest (AESIs)
- Amcenestrant predose concentrations

Statistical methods:

Main analysis population:

• Intent-to-treat (ITT) population: All participants who signed the informed consent form (ICF) and for whom there is a confirmation of successful allocation of a randomization number by IRT. Participants will be analyzed according to the treatment arm assigned at randomization. This is the primary population for all efficacy parameters.

• Safety population: All participants who signed the ICF and for whom there is a confirmation of successful allocation of a randomization number by IRT and who took at least 1 dose of study intervention. Participants will be analyzed according to the treatment arm they actually received. This population is the primary population for the analysis of all safety parameters.

Analysis of primary endpoint:

Primary efficacy analysis consisted of IBCFS comparison between the amcenestrant arm and the tamoxifen arm through a logrank test procedure stratified by the stratification factors (except geographic region to minimize the risk of power loss due to large number of strata and potentially low number of events in some strata) as entered in the IRT. A one-sided Type I error rate of 2.5% was used for statistical testing.

The HR estimates and corresponding confidence intervals were provided using the Cox proportional hazard model stratified by the same stratification factors as those used for the logrank test described above. The IBCFS quantiles and IBCFS rates at different time points (calculated using the Kaplan-Meier methods) as well as corresponding 95% CIs were presented by treatment arm. The Kaplan-Meier IBCFS curves were also provided.

Analysis of main secondary endpoints:

Key secondary endpoint (IDFS)

Same statistical methods as defined for the IBCFS was used. To ensure a strong control of the overall Type I error rate at a one-sided 2.5%, a hierarchical testing strategy was used. In other words, comparison between arms on the IDFS was performed only if the primary analysis of the IBCFS was statistically significant.

Other secondary efficacy endpoints

For the following time to event secondary endpoints (DRFS, LRRFS, OS), same statistical methods as defined for the IBCFS and IDFS endpoints were used, with the exception that no statistical testing were performed.

For the endpoint BCSS, the HR estimate and corresponding 95% two-sided confidence intervals (CIs) were provided by using Fine and Gray model accounting for competing risks and stratified by the stratification factors (except geographic region) as entered in the IRT. The cumulative incidence of breast cancer-related deaths at different timepoints (calculated using the cumulative incidence function method) as well as 95%CIs were presented by treatment arm. The corresponding BCSS rates and 95%CIs were computed as “1 minus cumulative incidence function”. The cumulative incidence curves were also provided.

Analysis of safety endpoints

Adverse events were coded according to MedDRA and graded according to the NCI-CTCAE v5.0. Summaries were provided for all grades combined and for Grade ≥3 (including Grade 5). Adverse event incidence table were provided by treatment group for all types of treatment-emergent adverse events (TEAEs): all TEAEs, all treatment emergent AESI (defined with a preferred term (PT) or a prespecified grouping), all treatment emergent SAEs, all TEAEs related to IMP, all TEAEs leading to permanent treatment discontinuation and all TEAEs leading to dose modification. Death was also analyzed.

Hematology and clinical chemistry results were graded according to the NCI-CTCAE v5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the on-treatment period were provided on the safety population.

The study was terminated early by the Sponsor on 17 August 2022, due to discontinuation of overall clinical development program of amcenestrant (SAR439859). A total of 3 patients were randomized, instead of the planned 3738 patients. Ongoing patients were not allowed to continue the study and were instructed to move to appropriate standard of care therapy. The primary and secondary objectives were not assessed as planned. The planned statistical analyses were changed before the database lock of the study according to the availability and reliability of the data. All planned figures, statistical modeling, and inferential statistical tests were removed, only descriptive statistics (participants disposition, demography, disease characteristics, deviations, exposure and AEs) were provided as tables and/or listings.

Summary results:

Protocol deviations

Two participants out of 3 randomized participants (66.7%) had at least 1 critical or major deviation. The first deviation was due to the randomization procedure error (incorrect stratification of a participant by duration of AI therapy), and the second was due to the enrollment of a participant with an exclusion criteria (Grade 3 diabetes that was considered uncontrolled).

Demographic and other baseline characteristics:

Demographic:

The median age for participants was 59.0 years (ranging from 55 – 65 years) with 2 participants below 65 years old and 1 between 65-85 years old. All 3 (100%) participants were female. All participants had an ECOG performance status (PS) of 0 and were ER positive. Of the 3 participants, 2 (66.7%) had a negative PgR status and 1(33.3%) had a positive PgR status. In regard to HER2 status, 1 (33.3) participant had a IHC score of 1+ and FISH not performed, and 2 (66.7%) participants had a IHC score of 2+ and FISH- (Table 1).

At initial diagnosis, 2 (66.7%) participants had Stage IIB disease, and 1 participant had Stage IIIA disease. For the primary tumor (T category), 2 participants were categorized as pT2 and 1 participant was pT3. For lymph nodes (N category), 2 participants were categorized as pN1 and 1 was categorized as pN1a (Table 2).

Table 1 - Summary of demographic and other baseline characteristics - Randomized population

	Tamoxifen (N=0)	Amcenestrant 200 mg (N=3)	All (N=3)
Age (years)			
Number	0	3	3
Mean (SD)		59.7 (5.0)	59.7 (5.0)
Median		59.0	59.0
Min ; Max		55 ; 65	55 ; 65
Age group (years) [n(%)]			
Number	0	3	3
<65	0	2 (66.7)	2 (66.7)
[65-85[	0	1 (33.3)	1 (33.3)
≥85	0	0	0
Sex [n(%)]			
Number	0	3	3
Male	0	0	0
Female	0	3 (100)	3 (100)
Race [n(%)]			
Number	0	3	3
White	0	0	0
Black or African American	0	0	0
Asian	0	1 (33.3)	1 (33.3)
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Multiple	0	0	0
Unknown	0	1 (33.3)	1 (33.3)
Not Reported	0	1 (33.3)	1 (33.3)
Ethnicity [n(%)]			
Number	0	3	3
Hispanic or latino	0	2 (66.7)	2 (66.7)
Not Hispanic or latino	0	1 (33.3)	1 (33.3)
Not Reported	0	0	0
Unknown	0	0	0
ECOG performance status [n(%)]			
Number	0	3	3
0	0	3 (100)	3 (100)
Baseline Weight (kg)			
Number	0	3	3

Mean (SD)		63.87 (12.05)	63.87 (12.05)
Median		63.50	63.50
Min ; Max		52.0 ; 76.1	52.0 ; 76.1
Baseline Weight by category (kg)			
Number	0	3	3
<50	0	0	0
[50-100[	0	3 (100)	3 (100)
≥100	0	0	0
HER2 status (based on local assessment) [n(%)]			
Number	0	3	3
1+	0	1 (33.3)	1 (33.3)
2+	0	2 (66.7)	2 (66.7)
HER2 status: details (based on local assessment) [n(%)]			
Number	0	3	3
IHC 1+ and FISH not performed	0	1 (33.3)	1 (33.3)
IHC 2+ and FISH -	0	2 (66.7)	2 (66.7)
ER status (based on central assessment) [n(%)]			
Number	0	3	3
Positive	0	3 (100)	3 (100)
PgR status (based on central assessment) [n(%)]			
Number	0	3	3
Negative	0	2 (66.7)	2 (66.7)
Positive	0	1 (33.3)	1 (33.3)
ECG result [n(%)]			
Number	0	3	3
Abnormal	0	2 (66.7)	2 (66.7)
Normal	0	1 (33.3)	1 (33.3)
Specify abnormality [n(%)]			
Number	0	2	2
Incomplete Left Bundle Branch Block	0	1 (50.0)	1 (50.0)
Left Ventricular Hypertrophia	0	1 (50.0)	1 (50.0)
Missing	0	1	1
FFPE Sample collected [n(%)]			
Number	0	3	3
Yes	0	3 (100)	3 (100)
Has subject ever been infected by SARS-CoV-2 (COVID-19) [n(%)]			

Number	0	3	3
No	0	2 (66.7)	2 (66.7)
Yes	0	1 (33.3)	1 (33.3)

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Table 2 - Disease characteristics at baseline - Randomized population

	Tamoxifen (N=0)	Amcenestrant 200 mg (N=3)	All (N=3)
Primary site [n(%)]			
Number	0	3	3
Breast	0	3 (100)	3 (100)
Stage Group [n(%)]			
Number	0	3	3
IIB	0	2 (66.7)	2 (66.7)
IIIA	0	1 (33.3)	1 (33.3)
T category [n(%)]			
Number	0	3	3
pT2	0	2 (66.7)	2 (66.7)
pT3	0	1 (33.3)	1 (33.3)
N category [n(%)]			
Number	0	3	3
pN1	0	2 (66.7)	2 (66.7)
pN1a	0	1 (33.3)	1 (33.3)
M category [n(%)]			
Number	0	3	3
cM0	0	3 (100)	3 (100)

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Exposure:

The median duration of IMP exposure was 126 days. The exact duration of IMP exposure for each participant was 8, 126, and 155 days.

Safety results:

Of the 2 (66.7%) participants that had at least 1 TEAE, 1 (33.3%) participant had TEAEs related to amcenestrant (Table 3). The TEAEs related to amcenestrant were headache and dry mouth. No deaths, treatment-emergent SAEs, TEAEs leading to permanent study drug discontinuation or treatment-emergent AESIs were reported during the course of this study.

The number of participants with TEAEs by primary SOC and PT are listed in Table 4. The reported TEAEs by PT were dry mouth, nail infection, anorexia, glucose intolerance, myalgia, and headache. All TEAEs were reported by 2 (66.7%) participants.

Table 3 - Overview of treatment-emergent adverse events (TEAEs) - Safety population

n (%)	Tamoxifen (N=0)	Amcenestrant 200 mg (N=3)
Participants with any TEAE	0	2 (66.7)
Participants with any grade ≥ 3 TEAE	0	0
Participants with any grade 5 TEAEa	0	0
Participants with any treatment emergent SAE	0	0
Participants with any TEAE leading to permanent study intervention discontinuation	0	0
Participants with any treatment-related TEAE	0	1 (33.3)

TEAE: Treatment emergent adverse event

aGrade 5 TEAE occurring during the treatment period

MedDRA dictionary version 25.1, NCI CTCAE version 5.0

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Table 4 - Number (%) of patients with TEAEs by primary SOC and PT (worst grade by patient) - Safety population

PRIMARY SYSTEM ORGAN CLASS **Preferred Term n(%)**	**Tamoxifen (N=0)**	**Amcenestrant 200 mg (N=3)**
Any event	0	2 (66.7)
GASTROINTESTINAL DISORDERS	0	1 (33.3)
Dry mouth	0	1 (33.3)
INFECTIONS AND INFESTATIONS	0	1 (33.3)
Nail infection	0	1 (33.3)
METABOLISM AND NUTRITION DISORDERS	0	1 (33.3)
Anorexia	0	1 (33.3)
Glucose intolerance	0	1 (33.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (33.3)
Myalgia	0	1 (33.3)
NERVOUS SYSTEM DISORDERS	0	1 (33.3)
Headache	0	1 (33.3)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term

MedDRA dictionary version 25.1, NCI CTCAE version 5.0

n (%) = number and percentage of participants with at least one TEAE

Note: Table sorted by SOC internationally agreed order and PT by alphabetic order

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