AMENDED CLINICAL TRIAL PROTOCOL 01

Protocol title:	**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**
Protocol number:	**EFC16133/BIG 20-01/AFT-55/EORTC-2033**
Amendment number:	**01**
Compound number (INN/Trademark):	**SAR439859** **Amcenestrant/Not Applicable**
Brief title:	**Study of amcenestrant (SAR439859) versus tamoxifen for patients with hormone receptor-positive (HR+) early breast cancer, who have discontinued adjuvant aromatase inhibitor therapy due to treatment-related toxicity (AMEERA-6)**
Acronym:	**AMEERA-6**
Study phase:	**Phase 3**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
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Monitoring team's representative name and contact information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	All	05 May 2022, version 1 (electronic 1.0)
Original Protocol	All	02 September 2021, version 1 (electronic 2.0)

Amended protocol 01 (05-May-2022)

This amended protocol 01 (Amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The objective of this first amended protocol is to modify the protocol:

- Following ethical committees and health authorities' requests.
- Clarifications due to questions from sites of eligibility criteria related to disease characteristics, prior/concomitant therapy and disease assessment, biological samples and storage.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Entire document	Regarding human epidermal growth factor receptor 2-negative, the word was "receptor" added as missing in the original text.	Clarifications across several sections
	Correction of typographical errors and minor inconsistencies	Correction
Section 1.1-Synopsis	In the section Analysis of primary endpoint, the level of confidence "95% two-sided" for the confidence interval of the hazard ratio removed	Clarification considering that the level of confidence will be adjusted for the Type 1 error spent at interim analysis and final analysis

Section # and Name	Description of Change	Brief Rationale
Section 1.3-Schedule of activities	1) assessments during the follow up period will be done Q12 months after last IMP dose; 2) FSH and estradiol are collected at screening for eligibility and to confirm the menopausal status; 3) to measure bone mineral densitometry other quantitative methods are allowed; 4) for disease staging, PET-CT is permitted; 5) at screening staging of disease is needed for patients at highest risk of recurrence as outlined in I08; 6) PGIC, MMAS8 not performed during follow-up period; 7) Plasma biomarkers-Central labs and Optional blood samples for future research at C2D1 are collected before IMP administration.	Clarifications and cleaning of inconsistencies
Section 1.3-Schedule of activities	1) addition of gynaecological examination one year after randomization and annually until end of treatment. 2) The frequency of pregnancy testing was increased to every 12 weeks from visit 11 until the end of the mandatory period of contraception as per Appendix 4: either onsite or at home.	1) To monitor the risk of endometrial changes due to tamoxifen and to be compliant with Korean competent authorities. 2) The end of the mandatory period of contraception is aligned with CMPH recommendation regarding fetal toxicity risk of tamoxifen to be compliant with French competent authorities.
Section 2.3	Eye disorder was added in the table as a potential risk of clinical significance of tamoxifen.	For the purpose of tamoxifen risk mitigation on eye disorder and to be compliant with Belgian and French competent authorities.
Section 5.1: Inclusion criteria	I02: rephrased to clarify axillary lymph nodes testing for ER and/or PgR (if done, must be positive to be eligible).	Clarification.
Section 5.1: Inclusion criteria	I03: - Addition of unknown HER2 status as eligible. - Enrollment replaced by randomization.	To allow patients who may have unknown HER2 status to enroll.
Section 5.1: Inclusion criteria	I04: - Participants could have had adjuvant radiation if indicated. - TNM staging for participants with upfront surgery - In case of neoadjuvant systemic therapy, participants must have stage II-III disease based on clinical staging (cTNM) and residual nodal disease after definitive breast surgery (ypN1-3). - Participants with only residual micro-metastatic disease (N1mic) or isolated tumor cells (ITCs) in the axillary lymph nodes are not eligible Note: the One-Step Nucleic Acid Amplification (OSNA) method is acceptable for sentinel lymph-node assessment.	Clarification and detail about staging based on type of treatment patient received (neoadjuvant vs adjuvant).

Section # and Name	Description of Change	Brief Rationale
Section 5.1: Inclusion criteria	I05: Inclusion criterion regarding the AI(s) previously received rephrased.	Clarification
Section 5.1: Inclusion criteria	I07: - The wash-out period after CDK4/6 is at least 4 weeks between the last dose and randomization. - Prior treatment with PARP inhibitors or other oral anticancer agents is allowed but must have wash-out period of at least 2 weeks between the last dose and randomization	Clarification related to CDK 4/6 washout prior to randomization to be compliant with the French Competent Authorities. Prior oral anticancer agents allowed with a washout of 2 weeks, PARP inhibitors specifically mentioned given recent approval of adjuvant PARP inhibitors in high risk early breast cancer.
Section 5.1: Inclusion criteria	I08: rephrased	Clarification
Section 5.1: Inclusion criteria	I11: - Recommendation to test FSH and estradiol for participants post bilateral ovarian ablation through pelvic radiotherapy - For contraception, inclusion of reference to Appendix 4 (contraception guidelines);	Confirmation of postmenopausal status. Clarification to be compliant with the French Competent Authorities.
Section 5.2: Exclusion criteria	E01: rephrased	Clarification (no change in content)
Section 5.2: Exclusion criteria	E02: specified **"**known**"** active hepatitis	Clarification that if active hepatitis is **"**known**"** patient is excluded; hepatitis serologies are not required but may be obtained per PI discretion and clinical decision making (no change in content)
Section 5.2: Exclusion criteria	E03: criterion related to prior breast cancer history rephrased	Clarification (no change in content)
Section 5.2: Exclusion criteria	E08: rephrased and enrollment replaced by randomization.	Clarification
Section 5.2: Exclusion criteria	E09: prior treatment for bone health, risk reduction, or a prior breast cancer with raloxifene or tamoxifen (SERM) is permitted if discontinued at least 3 years before diagnosis of current breast cancer.	Modification of prior treatment to allow inclusion of participants who received SERMs as long as there is a window of 3 years between completion of SERM and current breast cancer diagnosis
Section 5.2: Exclusion criteria	E12: Washout period of 2 weeks added for OATP1B1/1B3 sensitive substrates drugs.	Clarification
Section 5.2: Exclusion criteria	E13: Wash out period for strong CYP3A4 inducers modified for 3 weeks. E14 and E15: removal of 5 elimination half-lives.	Clarification to delete 5 elimination half-lives and have a period to simplify

Section # and Name	Description of Change	Brief Rationale
Section 5.2: Exclusion criteria	E17: restriction regarding blood transfusion not permitted within 2 weeks prior to randomization;	To ensure blood counts are not within range for study due to blood transfusions, for example patients who may have residual toxicity from chemotherapy
Section 5.2: Exclusion criteria	E20: total bilirubin cut-off increased to >1.5 x ULN	To align with current clinical pratice
Section 6.1.4	No specific water requirement (noncarbonated removed)	Clarification (more water initially required for studies with significant PK monitoring; in this study sparse PK studies will be done and no specific water requirement is needed)
Section 6.3	The randomization will not be possible if study treatment and ER/PgR central results are not available at site. For unblinding, actions for emergency unblinding and unblinding after the first IBCFS event clarified	Clarification
Section 6.4	IMPs omissions and NIMP delays/omissions will be recorded in the CRF.	Clarification
Section 6.8	Any concurrent anti-cancer treatment (surgery, radiotherapy, systemic therapy) except for participants diagnosed during the study with a second primary malignancy not requiring systemic therapy (ie, chemotherapy, hormonal therapy, targeted therapy, etc) and for whom study treatment is temporarily suspended to allow local treatment (surgery and/or radiation) A list of strong CYP3A inducers was added.	In this trial other anticancer treatment than the study treatment is not permitted Clarification
Section 8.1	This section is rephrased, restructured and revised for consistency with schedule of assessments.	Clarifications and cleaning of inconsistencies
Section 8.2.1	Gynecological examination added	Request from Korean competent authorities to add gynecologic exams based on endometrial risks from tamoxifen
Section 8.2.2	Body temperature added to vital signs	Request from United Kingtom competent authority to ensure there are no signs of infection.
Section 8.3.1	All AEs and SAEs will be collected from the signature of ICF to 30 days after last IMP dose. After this period, all ongoing related AEs, all ongoing SAEs regardless of relationship with study treatment, and all new related AEs (serious or nonserious), are to be reported and followed up until resolution or stabilization.	Clarification
Section 8.4	Approximately 300 plasma samples will be collected	Increase the number of plasma samples in order to have 100 samples from Chinese patients and 200 from other countries

Section # and Name	Description of Change	Brief Rationale
Section 8.5	The gDNA material will be only used for the elimination of the non-somatic variants of the tumor genetic studies and it will not be subject of any study by itself. The genetic findings will be reported to the sites.	Clarifications
Section 8.6.2	The total number of blood s-monovette edta 1,2 mL tubes for plasma collected C2 and C7 will be 300.	Increase the number of plasma samples in order to have 100 samples from Chinese patients and 200 from other countries
Section 8.9 and Section 10.5 Appendix 5	Biological samples will be stored for 15 years. Data related to future research will be stored for 25 years.	Clarifications
Section 9.2.1	In Table 7 Timing of analyses, the word “approximately” has been added in the column “Number of events required”	Clarification if the number of events required is not reached in a reasonable timeframe
Section 9.2.2	In the Table 8 and in the text, the level of confidence “95%”/”95 two-sided” for the confidence interval of the hazard ratio removed, respectively.	Clarification considering that the level of confidence will be adjusted for the Type 1 error spent at interim analysis and final analysis
Section 9.3	Cumulative probability to stop for futility under IBCFS HR = 0.76 (false negative rate) added in Table 11 - Summary of IBCFS summary	Request from French competent authorities
Section 10.2 Appendix 2	Other blood tests will include FSH, estradiol, PT/INR and bone turnover markers. If local lab cannot measure bone tumor markers, samples will be shipped to a central lab	Clarifications
Section 10.4 Appendix 4	This appendix includes information on contraception for pre/perimenopausal participants. Both male and female participants must agree to be on GnRH. Female patients must agree to use highly effective methods of contraception during the treatment period until the end of relevant systemic exposure (ie, 5 times of the longest IMP half-life (tamoxifen) plus 6 months period, which corresponds to ~9 months for tamoxifen as per CMDh guidance. Male participants without prior orchiectomy must keep contraceptive measures until 160 days after last IMP dose. Collection of pregnancy information over a period of 6 to 8 weeks however it may be longer if required by local regulations.	Update for female contraception period requested by French ethics committee. Update for male contraception period requested by Belgium and United Kingdom competent authorities.
Section 10.8 Appendix 8	For CHINA: a total of100 plasma samples was added for PK analysis. Genetic analyses and biomarker research for FFPE at screening is not applicable.	Clarifications
Section 10.10.1 Appendix 10	New information regarding Gr 4 toxicity	Update of safety guidelines requested by French competent authorities.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

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

Brief title:

Study of amcenestrant (SAR439859) versus tamoxifen for patients with hormone receptor-positive (HR+) early breast cancer, who have discontinued adjuvant aromatase inhibitor therapy due to treatment-related toxicity (AMEERA-6)

Rationale:

Selective estrogen receptor degraders (SERDs) are competitive estrogen receptor (ER) antagonists that also induce conformational ER changes which lead to the degradation of ER via a ubiquitin proteasome system. The unique dual function of SERDs (ER antagonism and depletion) may enable them to block ER signaling in cellular settings where other endocrine agents, such as tamoxifen or aromatase inhibitors (AIs) have failed.

The purpose of the proposed study is to demonstrate the superiority of a new oral SERD, amcenestrant (SAR439859) versus tamoxifen on invasive breast cancer-free survival (IBCFS) in patients with hormone-receptor positive (HR+) early breast cancer who have discontinued adjuvant AI therapy due to treatment-related toxicity. For this population, there are currently limited treatment options after AI discontinuation, which include either switching to another AI which may have similar side effects, or to tamoxifen. It is estimated that about 30% of the patients treated with aromatase inhibitor discontinue their adjuvant therapy and that 22% discontinue during the first year (1, 2).

Objectives and endpoints:

Objectives	Endpoints
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	• IBCFS is defined according to Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP) criteria version 2.0 (3) 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**	
• 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	• IDFS is defined according to STEEP criteria (4) 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

Objectives	Endpoints
Other secondary endpoints	
• To evaluate the distant recurrence-free survival (DRFS) in both treatment arms	• DRFS is defined according to STEEP criteria (4) 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).
• To evaluate the locoregional recurrences-free survival (LRRFS) in both treatment arms	• 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).
• To evaluate the overall survival (OS) in both treatment arms	• OS is defined as the time interval from the date of randomization to the date of death due to any cause.
• To evaluate the breast cancer-specific survival (BCSS) in both treatment arms	• BCSS is defined as the time interval from the date of randomization to the date of death attributable to breast cancer cause
• To evaluate patient-reported overall treatment-related side effect bother, treatment-related symptoms, and quality of life in both treatment arms	• 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
• To evaluate safety in both treatment arms	• Adverse events (AEs)/serious adverse events (SAEs), laboratory abnormalities and adverse events of special interest (AESIs).
• To characterize the pharmacokinetics (PK) of amcenestrant	• Amcenestrant predose concentrations

For China please see Section 10.8 [Appendix 8] for details.

Overall design:

This is 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 will have 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 have discontinued adjuvant AI therapy due to treatment-related toxicity will enter the screening period to assess their eligibility.

Participants still on AI treatment may enter the screening period for central confirmation of biomarkers and screening imaging assessments. The other assessments/questionnaires required before randomization will be performed/completed when patient is off the AI therapy.

All eligible participants for whom ER and PgR status have been centrally confirmed will be 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 will also receive the matching placebo of the other treatment under evaluation. Both treatments are given orally.

The study population will be 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 will be 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

During the treatment period, men and pre/perimenopausal women will receive GnRH analogs as approved in the respective countries.

Participants will receive their assigned treatment for the planned duration of 5 calendar years or until diagnosis of disease recurrence per IBCFS definition or any other withdrawal criterion whichever occurs first.

Early discontinuation during the active study treatment period will be left at the investigator's discretion.

Extended adjuvant endocrine therapy upon completion of study treatment is allowed, but treatment will not be provided by the sponsor. Treatment recommendation should be considered on an individual patient basis taking into consideration clinico-pathologic characteristics, patient's preferences, and total duration of adjuvant endocrine therapy at the time of study treatment completion or discontinuation. When extended adjuvant endocrine therapy is considered, treatment options include adjuvant tamoxifen or adjuvant aromatase inhibitor.

In case of diagnosis of second non-breast primary invasive cancers, the decision to keep the patient on protocol treatment is based on clinical judgement of the treating physician. Patients diagnosed with a second primary malignancy not requiring systemic therapy (ie, chemotherapy, hormonal therapy, targeted therapy, etc) and with no evidence of breast cancer recurrence may continue with study drug treatment according to the protocol and schedule of assessment, if considered by the investigator to be in the patient's best interest, whenever possible. Study treatment may be temporarily suspended to allow for local treatment (surgery and/or radiation) of the second non-breast primary invasive cancer; in this situation, the maximally allowed period of protocol treatment discontinuation should not exceed a total of 3 months in any 12-month time period.

Participants discontinuing or completing the active study treatment period will be followed up to 10 years from randomization, except in case of premature study termination due to one of the following reasons: withdrawal of consent, loss to follow-up or death.

An Independent Data Monitoring Committee (IDMC) will monitor the safety data on a periodic basis. The IDMC will make recommendations as to whether the trial should continue based on ongoing reviews of safety data. The IDMC will also evaluate efficacy at the interim analyses and make a recommendation regarding study continuation based on observed results of the current study and/or external study data generated with amcenestrant. The IDMC procedures will be described in the full protocol and detailed in the IDMC charter and will be approved by IDMC members.

A Study Steering Committee will supervise the progress of the trial, review relevant information that may affect the study conduct as well as review and take decisions to act on the IDMC recommendations.

Brief summary:

This is a parallel treatment, Phase 3, Participant, Investigator and Outcomes Assessor masked, 2 arms randomized study.

Number of participants:

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

Intervention groups and duration:

Participants will be randomly assigned (1:1) to either Arm A (experimental) or Arm B (control):

- Arm A: Amcenestrant (SAR439859) 200 mg + tamoxifen-matching placebo
- Arm B: Amcenestrant (SAR439859)-matching placebo + tamoxifen 20 mg

Treatments in both arms are given orally.

Participants will receive their assigned treatment for the planned duration of 5 calendar years or until the occurrence of any withdrawal criterion, whichever occurs first.

During the treatment period, men and pre/perimenopausal women will receive GnRH analogs as approved in the respective countries.

No dose reductions for amcenestrant and tamoxifen are permitted but dosing omissions are allowed in case of toxicity. Temporary study treatment interruption is also permitted in special circumstances as described in protocol Section 6.5.3.

Study intervention(s)

Investigational medicinal products (IMPs)

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

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

Tamoxifen and tamoxifen-matching placebo

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

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

Non-investigational medicinal products (NIMPs)

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

Statistical considerations

Sample size determination:

For IBCFS primary endpoint, a total of 568 IBCFS events will be needed to reject the null hypothesis using a log-rank test at the one-sided level of 2.5% and 90% power under the assumption of a hazard ratio (HR) of 0.76. Assuming proportional hazards under an exponential model and based on an anticipated 4-year IBCFS rate of 82% in the tamoxifen arm, this is expected to correspond to a 4-year IBCFS rate of 86% in the amcenestrant arm.

Based on piecewise enrollment assumption over 24-month period, an IBCFS cut-off date (COD) of 60 months after the first participant randomized and an annual dropout rate of 1%, a total of 3738 participants are expected to be randomized in a 1:1 ratio into the amcenestrant and tamoxifen arms.

The number of events/sample size calculation accounts for two interim analyses at 1/3 (non-binding futility only) and 3/4 (efficacy and non-binding futility) of the planned total number of events.

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 will consist 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% will be used for statistical testing.

The HR estimates and corresponding confidence intervals will be 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 will be presented by treatment arm. The Kaplan-Meier IBCFS curves will also be provided.

Analysis of main secondary endpoints:

Key secondary endpoint (IDFS)

Same statistical methods as defined for the IBCFS will be used. To ensure a strong control of the overall Type I error rate at a one-sided 2.5%, a hierarchical testing strategy will be used. In other words, comparison between arms on the IDFS will be performed only if the primary analysis of the IBCFS is 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 will be used, with the exception that no statistical testing will be performed.

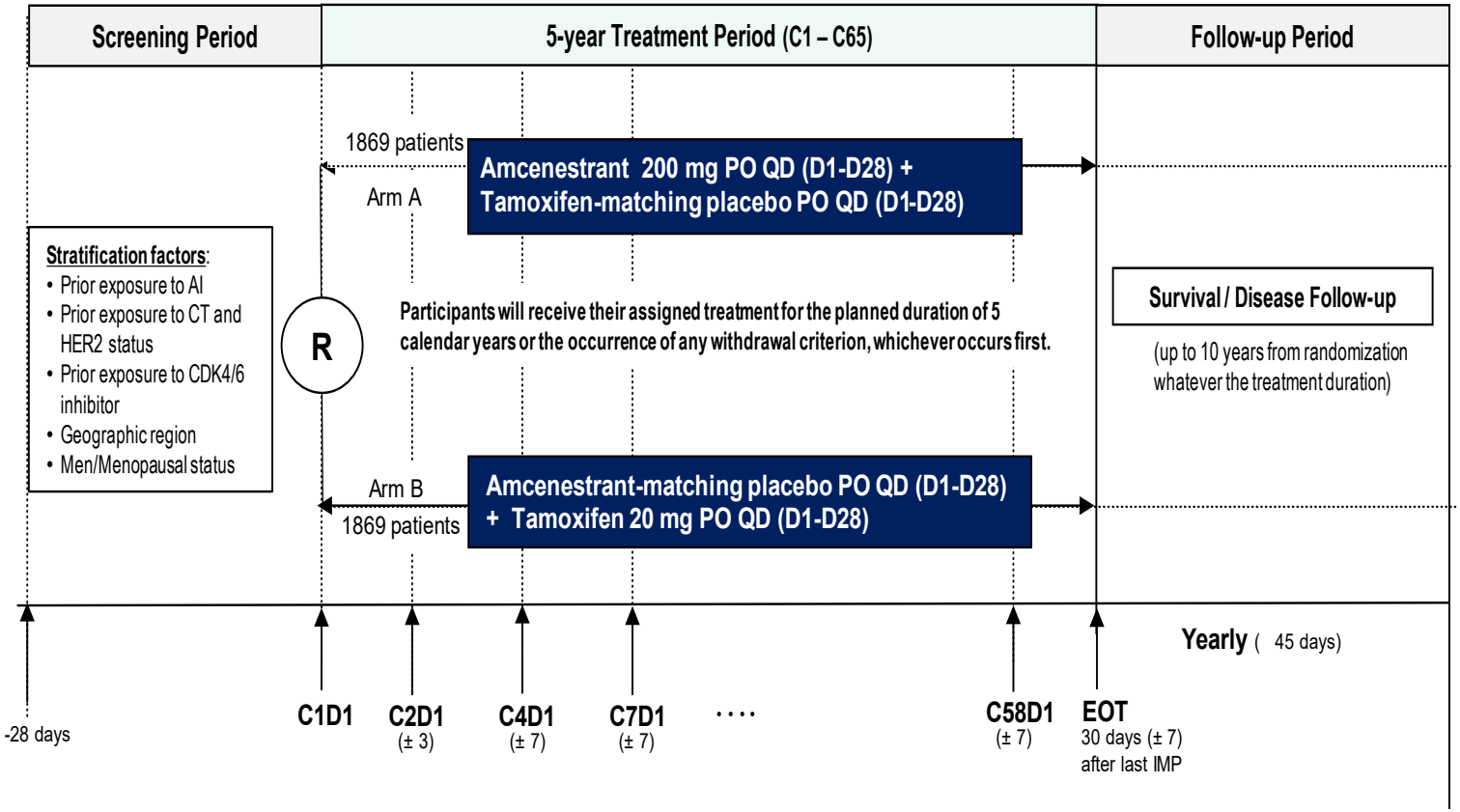
For the endpoint BCSS, the HR estimate and corresponding 95% two-sided confidence intervals (CIs) will be provided by using Fine and Gray model accounting for competing risks and stratified by the stratification factors (except geographic region) as entered in the IRT. The cumulative incidence of breast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

Analysis of safety endpoints

Adverse events will be coded according to MedDRA and graded according to the NCI-CTCAE v5.0. Summaries will be provided for all grades combined and for Grade ≥3 (including Grade 5). Adverse event incidence table will be provided by treatment group for all types of treatment-emergent adverse events (TEAEs): all TEAEs, all treatment emergent AESI (defined with a 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 will also be analyzed.

Hematology and clinical chemistry results will be 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 will be provided on the safety population.

Data Monitoring/Other committee: Yes



AI = aromatase inhibitor; C = Cycle; CT = chemotherapy; D = day; EOT = End of Treatment; IMP = investigational medicinal product; PO = per os; QD = once a day; R = randomization
A cycle is defined as a 28-day period.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Inclusion exclusion criteria / Informed consent	X								Informed consent (including genetic sampling) may be signed prior to D-28. Recheck clinical status before randomization and/or first dose of study medication. For patients still on AI at screening, inclusion/exclusion criteria should be evaluated when AI has been discontinued
Demography, medical/surgical and disease history, prior cancer therapies	X								At screening visit only. Prior AI treatments (duration of treatment, reason(s) for discontinuation) to be collected. For patients still on AI at screening, medical history should be evaluated when AI has been discontinued.

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Vital signs, physical examination/ signs and symptoms	X	X[a]		X[b]			X	X	a. Visit 1 b. At visit 3 and then at each visit during the treatment period. Vital signs will be collected at baseline and during the treatment period.
ECOG performance status, body weight and height	X	X							Height will be collected at screening only. At baseline after patient has discontinued AI
Gynecological examination		X							From one year after randomization and annually until the end of treatment
Follicle-stimulating hormone (pre/perimenopausal women only)- Local labs	X								At screening for eligibility and to confirm the menopausal status. As per local regulations, to demonstrate postmenopausal status, serial measurements of FSH may be required.

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Estradiol (pre/perimenopausal women only) – Local labs	X[a]	X[b]							a. At screening for eligibility and to confirm the menopausal status b. At each visit during the treatment period, and at EOT. Female participant will be categorized as premenopausal or postmenopausal at the time of study entry. This designation shall not change during the course of study participation; even if a premenopausal woman will become postmenopausal during the course of study participation, she will still be categorized as premenopausal for the purposes of the study.

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Pregnancy test (pre/perimenopausal women only) – Local labs	X[a]	X[b]							a. Serum pregnancy test (β-hCG) to be done within 14 days before starting study treatment. b. Urine pregnancy test (dipstick) to be done for WOCBP: - At each visit from visit 1 to visit 10 - Every 12 weeks from visit 11 until the end of the mandatory period of contraception as per Appendix 4: either onsite or at home

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Laboratory assessments – Local labs	X[a]	X[b]							Hematology, biochemistry panels and coagulation: a. To be performed at screening within 7 days of Cycle 1 D1 after patient has discontinued AI. b. At each visit during the treatment period, at EOT, and as clinically indicated. Lipids assessments on Visit 1, Visit 3, Visit 4, and as clinically indicated.

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Bone mineral densitometry) / Dual-energy X-ray absorptiometry (DXA)	X[a]	X[b]							a. Screening: to be done if not already done in the past 12 months prior to randomization. b. Post baseline: every 2 years from randomization (+/-1 month) until end of follow -up period Other quantitative methods giving similar T-score values, including ultrasound bone densitometry and QCT (quantitative computerized tomodensitometry) are also accepted.
Bone Turnover Markers (CTX, P1NP) – Local labs	X[a]	X[b]							a. Screening: to be done if not already done in the past 12 months prior to randomization. b. During the treatment period: every 2 years from randomization (+/-1 month)
12-lead ECG	X						X		Screening (after patient has discontinued AI), EOT and as clinically indicated

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Randomization	X								Eligibility criteria data collection and central confirmation of ER and PgR biomarkers to be completed prior to IRT randomization call
Study Treatment Administration:									
IMP dispensation call		X		X	X	X[a]			a. Visit 16 (C58): IMP dispensation from C58 to C65, ie, 32 weeks
amcenestrant + tamoxifen-matching placebo		Once daily ←→							
tamoxifen + amcenestrant-matching placebo		Once daily ←→							
NIMP: GnRH analog		←→							- Goserelin or other GnRH analog approved for use in early breast cancer as per site/ country availability - In men and pre/perimenopausal women

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
AE/SAE review	←==========							X (ongoing related AEs, AESI, ongoing SAEs at EOT and new related AE/SAEs)	
Concomitant medication review	←==========							X (related to AE/SAEs listed above)	From the date of informed consent form up to 30 days after the last dose of study treatment
Disease assessments:									
Disease recurrence assessment	X								At every visit and as clinically indicated until the detection of locoregional recurrence and distant recurrences (whichever comes last) or end of follow-up period, whichever comes first.

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Mammogram	X[a]	X[b]							a. Screening: to be done if not already done in the past 6 months prior to randomization. If local investigator plans to use MRIs instead of mammograms during the study, MRI will have to be performed at baseline b. Post baseline: yearly from randomization (±30 days), and as clinically indicated until the detection of locoregional recurrence and distant recurrences (whichever comes last) or end of follow-up period, whichever comes first.

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Radionuclide Bone Scan Whole Body; CT Scan / MRI /PET-CT Ultrasound of Chest, Abdomen, Pelvis or any clinically indicated sites of disease; Clinical evaluation of superficial disease	(X[a])	(X[b])							a. Screening: to be done for patients at highest clinical risk for disease recurrence as outlined in I 08 (Section 5.1), for patients with stage IIIA or higher as clinically indicated. b. Post baseline: to be done as clinically indicated until the detection of locoregional recurrence and distant recurrences (whichever comes last) or end of follow-up period, whichever comes first.
Biopsy (disease recurrence proof)		(X)							Disease recurrence should be confirmed histologically whenever possible. For the locoregional recurrence including skin recurrence it is strongly recommended to perform a biopsy unless clinically contra-indicated.

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Overall Survival Follow-up								X	After discontinuation of study treatment, post-study survival status (including post-study anticancer therapies; disease recurrence for patients who complete or prematurely discontinue study treatment without disease recurrence) will be collected
Electronic PRO measures:									
EORTC QLQ-C30, EORTC QLQ-BR23, EORTC-QLQ-IL127, EQ-5D-5L, PGIS		X[a]	X[b]						a. Data collected prior to first IMP intake on device at site on D1 C1 or earlier if patient has no unrecovered acute toxic effects of prior AI therapy (see exclusion criteria 6). b. At each visit after the 1st cycle (D1 C2-C58) during the treatment period, at EOT, and at the first two post-treatment follow up visits. Data collected on device at site.

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
PGIC, MMAS-8			X						At each visit starting after the 1st cycle (D1 C2-C58) during the treatment period and at EOT. Data collected on device at site.
FACT-GP5, PRO-CTCAE items		X[a]	X[b]						a. Data collected prior to first IMP intake on device at site on D1 C1 or earlier if patient has no unrecovered acute toxic effects of prior AI therapy (see exclusion criteria 6). b. Data collected on device at home weekly in the first 6 weeks (+/-1 day) and every cycle on D1 C3-C6 (+/-7 days). Data collected on device at site at each visit starting after the 6th cycle (D1 C7-C58) during the treatment period, at EOT, and at the first two post-treatment follow up visits.

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
Samples for Translational research:									
FFPE tumor tissue	X[a]						X[b] (optional)		Refer to Section 8.6.2 for details a. Most recent archived FFPE biopsied tumor tissue samples b. Collected at EOT for patients who discontinued treatment due to disease recurrence
Plasma biomarkers – Central labs		X[a]	X[a]				X[b]		Refer to Section 8.6.2 for details a. Pre-dose b. Collected at EOT for patients who discontinued treatment due to disease recurrence
Blood sample for genomic DNA – Central labs		X							Refer to Section 8.5 and Section 8.6.2 for details Pre-dose C1D1 after patient has discontinued AI
Blood sample for pharmacokinetics – Centralized assay			X[a]		X[b]				Refer to Section 8.4 and Section 8.6.2 for details a. At pre-dose b. Samples to be taken at pre-dose C7, C13 and C25

Procedure	**Screening Period**	**Treatment Period** [5 years **– C1-C65**]					**EOT**	**Follow-up Period**	**Notes**
Patient Visit #	**0**	**1**	**2**	**3**	**4-10** Q12 weeks	**11-16** Q24 weeks	**17**	**≥18**	
Patient Cycle Visit #	Baseline	**C1** D1	**C2** D1	**C4** D1	**C7, C10, C13, C16, C19, C22, C25** D1	**C28, C34, C40, C46, C52, C58** D1	D30 after last IMP dose	Q12 months after last IMP dose	
Time Window (day)	Up to 28 days before randomization	±3	±3	±7	±7	±7	±7	±45	
(Optional) Blood Samples for Future Research		X[a]	X[a]				X[b]		Refer to Section 8.6.2 for details a. Pre-dose b. Collected at EOT for patients who discontinued treatment due to disease recurrence

All study visits performed during treatment period and follow-up period are conducted on-site (in participants without disease recurrence). On-site visits could be substituted by remote visits in specific circumstances.

Screening: Routine baseline tests performed prior to ICF signature do not need to be repeated as long as they are within the screening defined timeframe. Informed consent should be signed before any study specific procedures. It can be signed more than 28 days prior to randomization. Screening time indicates in which timeframe exams used to support eligibility have to be done prior to randomization.
Randomization: To take place once the consented patient has completed all the necessary screening procedures and is deemed eligible for study entry by the Investigator or designee. All eligible patients must be randomized using IRT. Every effort should be made to start treatment within 3 working days of randomization.

Treatment period: A cycle is defined as a 28-day period. Men and pre/perimenopausal women will receive GnRH analog on D1 of the cycle.

Physical examination/ signs and symptoms evaluation: At a minimum, assessments of the cardiovascular system, pulmonary system, gastrointestinal system (including palpation of liver and spleen), examination of the skin, and breast exam (palpation of breast/chest wall, axillae, supra- and infraclavicular regions). Symptom-directed physical examinations should be performed at screening and at each subsequent visit.

Cycle 1 D1 refers to the day the patient receives the initial dose of IMP. Repeated evaluation of body weight, signs and symptoms, physical examination and laboratory tests is not necessary if performed within 7 days prior to1st IMP administration. If evaluation performed during screening is abnormal, repeated evaluation is recommended within 2 days prior to 1st IMP administration.

End of treatment (EOT): should be performed 30 days (±7 days) after the last IMP and prior to the initiation of any new anti-cancer therapy, whichever comes first.

Follow-up period: each participant will be followed from EOT to up to 10 years from randomization except in case of premature study termination due to one of the following reasons: withdrawal of consent, loss to follow-up or death.

PRO/HRQL assessments: EORTC-QLQ-C30, EORTC-QLQ-BR23, EORTC-QLQ-IL127, FACT GP5, EQ-5D-5L, PRO-CTCAE, PGIC, PGIS, and MMAS-8 to be administered to each study participant after informed consent. At each assessment time, PRO/HRQL to be administered prior to any treatment- or study- related activities, including administration of IMP, laboratory work, radiological assessments, discussion with the participant regarding their treatment or health status, and similar activities

Mammogram: It shall not include patients with prior bilateral mastectomy. In case of unilateral mastectomy, unilateral mammogram will be performed.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AI = aromatase inhibitor; C = cycle; COA = clinical outcomes assessment; COD = cut-off date; CT scan = computed tomography scan; CTX = C-terminal telopeptide; DNA = deoxyribonucleic acid; D = day; DXA = Dual-energy X-ray absorptiometry; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-5L = EuroQoL questionnaire with 5 dimensions and 5 levels per dimension; ER= estrogen receptor; FACT GP5 = Functional Assessment of Cancer Therapy – Item GP5; FFPE = formalin fixed paraffin embedded; FSH = follicle-stimulating hormone; GnRH= gonadotropin-releasing hormone; HRQL = health-related quality of life; IL127 = ad-hoc item list constructed from the EORTC item library; IMP = investigational medicinal product; IRT= interactive response technology; MRI = magnetic resonance imaging; MMAS = Morisky Medication Adherence Scale; NIMP = non-investigational medicinal product; PGIC = Patient Global Impression of Change scale- Side effects of treatment; PGIS = Patient Global Impression of Severity scale- Side effects of treatment; P1NP = Procollagen type I N-terminal propeptide; QLQ BR23 = EORTC QLQ breast cancer specific module; QLQ C30 = EORTC core quality of life questionnaire version 3; PRO = patient-reported outcome; PRO-CTCAE = patient-reported outcomes version of the common terminology criteria for adverse events; SAE = serious adverse event.

2 INTRODUCTION

Both endogenous and exogenous steroid hormones such as estrogen and progesterone are known to contribute to the pathogenesis of breast cancer. Clinical treatment decisions of breast cancer are commonly driven by tumoral expression of hormone receptors (HRs), namely ER and progesterone receptors (PgR), as well as expression of HER2. While breast cancer can be subdivided by numerous systems, the most clinically relevant subtypes are HR-positive, HER2-positive (HER2+), and triple-negative breast cancer. About 75% of breast cancers express estrogen ERα which is a hormone receptor that regulates gene transcription (5).

As estrogens have a major impact in breast cancer development and progression, endocrine treatment (ET) is an increasingly and systematically used treatment option as adjuvant (after surgery) or neoadjuvant (before surgery) therapy (6, 7, 8). The current ETs that are used in the adjuvant setting are tamoxifen, a selective ER modulator (SERM) that acts by blocking the ER, and the AIs (letrozole, anastrozole, and exemestane), which reduce estrogen levels by inhibiting the peripheral synthesis of estrogen (9, 10).

Amcenestrant is a potent, orally bioavailable, and selective ERα inhibitor that belongs to the SERD class of compounds. SERDs have the potential to block endocrine-dependent and endocrine-independent ERα signalling by ablation of ERα and have been recognized to offer a therapeutic approach to ERα positive breast cancer in both early-stage breast cancer and advanced breast cancer. Amcenestrant antagonizes the binding of estradiol to ER but also promotes the transition of ERα to an inactive conformation that leads to up to 98% receptor degradation at sub-nanomolar concentrations in cellular assays.

These dual properties of amcenestrant translate in a deeper inhibition of ERα pathways and a more effective anti-proliferative activity in ERα-dependent breast cancer cell lines driven by mutant or wild-type ERα compared to other ERα inhibitors.

Amcenestrant has the potential to provide effective and well-tolerated therapy for patients with early and advanced breast cancer with a convenient route of administration, oral (PO) versus intramuscular (IM), better bioavailability, and long-term maintenance of ER receptor blockade combined with a strong antitumor activity as compared to fulvestrant. A detailed description of the chemistry, pharmacology, pharmacokinetics, preliminary efficacy, and safety of amcenestrant is provided in the IB.

Fulvestrant is the only currently approved SERD for HR+, HER2- metastatic breast cancer. Fulvestrant is approved for the treatment of patients with advanced breast cancer (either as monotherapy or in combination with targeted anticancer drugs) but it is not indicated as adjuvant endocrine therapy for patients with early-stage breast cancer. Fulvestrant has shown clinical benefit in the treatment of breast cancer patients who have progressed during endocrine therapies such as tamoxifen or AIs. However, fulvestrant must be administered as a monthly IM injection of a 500 mg dose to each gluteus maximus. Although fulvestrant has served as an important proof of concept for the SERD approach, this therapy is limited by its poor pharmaceutical properties which necessitate intramuscular administration and limits the applied dose, exposure, and optimal receptor engagement.

2.1 STUDY RATIONALE

2.1.1 Study rationale and purpose

The purpose of the proposed study is to demonstrate the superiority of amcenestrant *versus* tamoxifen with regards to IBCFS in patients with HR+ early breast cancer who have discontinued aromatase inhibitor as adjuvant treatment due to treatment-related toxicities. For this population, there are currently limited treatment options after AI discontinuation, including switching to another AI which may have similar side effects, or switching to tamoxifen. This paucity of effective and tolerable options may contribute to early discontinuation of adjuvant endocrine therapy. Poor adherence has been shown to be associated with worse outcomes (11, 12). It is estimated that about 30% of the patients treated with aromatase inhibitor discontinue their adjuvant therapy and that 22% discontinue during the first year (1, 11). The primary endpoint of this study will be IBCFS defined as occurrence of first recurrence of the disease: ipsilateral or regional invasive, distant recurrence, contralateral invasive breast cancer and death.

2.1.2 Rationale for dose and regimen selection

2.1.2.1 AMEERA-1 trial

The Phase 1/2 first-in-human (FIH) dose escalation and expansion AMEERA-1 (TED14856) study with amcenestrant single agent, has been designed for women with heavily pretreated, postmenopausal advanced or metastatic HR+/HER2-, breast cancer.

A strong pharmacokinetic/pharmacodynamic relationship was established between amcenestrant plasma concentrations and associated ^{18}F-FES PET percent occupancy of the ER. Overall mean occupancy per patient was 95.6% and 94.0% with amcenestrant 400 mg QD and 150-600 mg QD, respectively. The recommended dose of amcenestrant was established at 400 mg once daily when used as monotherapy for the treatment of advanced breast cancer.

In AMEERA-1, the antitumor activity of amcenestrant as monotherapy was assessed in 59 evaluable patients (treated from 150 to 600 mg QD) as well as in a subset of patients naïve from targeted therapies and fulvestrant. In the overall study population, the best overall responses (BOR) based on RECIST 1.1 criteria were 5 confirmed partial responses (PR; 8.5%), 24 stable disease (SD; 40.7%) and 30 progressive disease (PD; 50.8%). The antitumor activity observed in this population of heavily pretreated patients showed durable control of the disease with a high rate of clinical benefit [CBR (CR + PR + SD ≥24 weeks) = 33.9%] (13).

Amcenestrant demonstrates a favorable safety profile. Limited treatment-emergent adverse events (TEAEs) related to amcenestrant as monotherapy were observed on AMEERA-1, all Grade 1 and 2, the most frequent being: hot flush, arthralgia, and constipation.

2.1.2.2 Antitumor activity of amcenestrant compared to fulvestrant

A comparison of the AMEERA-1 results with those of fulvestrant in the medical literature was undertaken in order to place the amcenestrant data in the context of historical data. A total of 4 comparative studies were selected wherein fulvestrant was given as monotherapy and in which study eligibility criteria excluded patients with prior targeted therapies (mTOR and CDK 4/6 inhibitors) and prior use of fulvestrant (14, 15, 16, 17). The objective response rate (ORR) and the CBR were indirectly compared with the recommended 500 mg dose of fulvestrant monotherapy in the second or third line setting among postmenopausal women with advanced/metastatic ER+/HER2− breast cancer and whose tumor responses were confirmed as per RECIST v1.1 in populations with measurable disease. The PALOMA-3 (13) and FAKTION (14) studies recruited women who had received up to 3 prior lines of endocrine therapy and the SOLAR-1 (15) and SANDPIPER (16) studies with up to 2 prior lines. The PALOMA-3 study excluded women who had received prior fulvestrant and CDK4/6, PI3K, and/or mTOR inhibitors. The FAKTION, SOLAR-1 and SANDPIPER studies excluded women who had received prior fulvestrant and PI3K inhibitors, and the SOLAR-1 and SANDPIPER studies also excluded women who had received prior mTOR inhibitors. All four comparator studies investigated less heavily pre-treated patients than in AMEERA-1. In these studies, the fulvestrant monotherapy ORR ranged from 10.9–16.2% and CBR ranged from 36.0-44.1% (18, 19, 20, 21). Meanwhile, the ORR and CBR in AMEERA-1 study in a similar subset population (14 patients who had not received prior therapy with fulvestrant, an mTOR inhibitor, or a CDK 4/6 inhibitor) compared favorably to these historical data with ORR of 21.4% and CBR of 64.3%.

Given the demonstrated antitumor activity and safety of amcenestrant in the treatment of advanced breast cancer, there is interest in whether amcenestrant may also offer an effective and safe treatment option in the adjuvant setting. In order to address the early-stage breast cancer population, short-term preoperative studies are considered as a validated strategy to provide rapid and cost-efficient proof-of-concept for novel treatment approaches by assessing the direct effects of the study treatment on the tumor tissue (22, 23). Detailed studies in the neoadjuvant setting in prospective randomized clinical trials have demonstrated the utility and validity of changes in Ki67 as a predictor of benefit from treatment and of long-term outcome (24, 25). For example, in the preoperative IMPACT study, suppression of Ki67 at 2 weeks was greater with anastrozole than with either tamoxifen or the combination of anastrozole plus tamoxifen, and this was correlated with recurrence-free survival (26, 27).

2.1.2.3 AMEERA-4 trial

AMEERA-4 (ACT16106) is a dedicated window-of-opportunity study with amcenestrant in pre-operative ER+/HER2- postmenopausal breast cancer patients. Data are not yet published.

AMEERA-4 study assessed two dose levels of amcenestrant (200 mg and 400 mg daily) as compared to letrozole 2.5 mg daily among participants with newly diagnosed ER+/HER2- breast cancer with highly proliferative tumors (Ki67 ≥15% at diagnosis by local assessment). Participants were equally randomized to the three study arms above and treated with 14 days of endocrine therapy immediately prior to breast surgery with a primary endpoint of change in Ki67 from baseline to Day 15. Central assessment of Ki67 was performed by two independent reviewers and the average value of these two reviewers at each timepoint was used for the primary

analysis. Ki67 change from baseline to Day 15 was analyzed based on an ANCOVA model of the log-proportional change from baseline (ie, $log\left(\frac{D15}{Baseline}\right)$), with treatment arm and log-Ki67 at baseline as fixed effect. Geometric LS-means and associated 95% confidence interval (CI) of the Ki67 relative reduction from baseline were obtained by back-transformation on the original scale. An administrative interim analysis was undertaken in April 2021 following the randomization of the first 63 patients. Regarding baseline characteristics of the study patients, there were no major imbalances noted between the study arms.

Regarding safety, among 62 patients exposed to the study treatment, no safety issues were observed: there were few low-grade events observed in each treatment arm and no participants discontinued treatment due to adverse events. The most frequent TEAEs during the on-treatment and post-treatment periods of 10% or greater frequency in any treatment arm, all low-grade (grades 1 and 2), were: hot flush (19.0%), diarrhea (14.3%), arthralgia (14.3%) and breast pain (14.3%) for letrozole 2.5 mg (N = 21); asthenia (10.0%) and hot flush (5.0%) for amcenestrant 200 mg (N=20); insomnia (14.3%), hot flush (9.5%) and arthralgia (4.8%) for amcenestrant 400 mg (N=21). Regarding the primary endpoint, among 55 patients with evaluable paired tumor biopsies, the geometric LS-means [95% CI] were: 72.04% [59.73%;80.59%] for letrozole 2.5 mg (N=18); 68.17% [54.13%;77.92%] for amcenestrant 200mg (N=18); 74.99% [64.30%;82.48%] for amcenestrant 400 mg (N=19). The specific amcenestrant target ER protein was scored by IHC (H-score). ER expression decreased on average (SD) by 67.1% (±32.6%) and 47.8% (±68.7%) in amcenestrant 200mg and 400mg, respectively. As expected, letrozole had limited impact on ER expression (4.8% (±11%)).

2.1.2.4 AMEERA-6 trial

While the pharmacodynamic activity and safety results from AMEERA-4 could support use of either amcenestrant 200 mg or 400 mg in the AMEERA-6 study (EFC16133), the lower dose of 200 mg is preferred given the proposed long-term exposure (5 years) in early breast cancer, in particular for these study participants who discontinued prior adjuvant AI due to treatment-related toxicities.

As letrozole was found to be significantly more active than tamoxifen in a neoadjuvant study including postmenopausal patients with ER+ and/or PgR+ ineligible for breast-conserving surgery (28) and amcenestrant preliminary results were comparable to letrozole in AMEERA-4, the proposed treatment with amcenestrant in AMEERA-6 is considered as appropriate.

In AMEERA-6 study, it is recommended to take amcenestrant with food in order to ensure favorable exposure for all patients, including those who may have lower absorption. This recommendation is supported by several food effect studies conducted during Phase 1 program on capsule or tablet formulations. The highest magnitude of food effect was 1.67-fold increase of Cmax and 1.77-fold increase of AUC with a moderate fat meal (400-500 Kcal containing approximately 9% protein, 27% lipids, and 64% carbohydrate) regardless of amcenestrant dose (200 to 600 mg) or formulation (capsule or tablet). In addition, recent data showed that a high fat meal (800 – 1000 Kcal containing approximately 15-19% protein, 60-63% lipids, and 25-31% carbohydrate) would increase Cmax by 1.25-fold and AUC by 1.71-fold for a single 400 mg dose. In repeated administration conditions, using a population model analysis, food effect accounted

for about 20% increase of the exposure. Using maximum food effect reported at higher dose in single dose studies, increase of exposure for a 200 mg dose remains within the range of highest exposure documented with 1200 mg single dose in healthy subjects and 600 mg QD or 300 mg BID in advanced cancer patients and is considered as safe.

2.2 BACKGROUND

Breast cancer is the most commonly diagnosed cancer and the second leading cause of death in women (29). In 2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. There are more lost disability-adjusted life years (DALYs) by women to breast cancer globally than any other type of cancer. Breast cancer occurs in every country of the world in women at any age after puberty but with increasing rates in later life (30). In the United States (US) in 2020, a total of 276 480 new cases of invasive breast cancer diagnosed in women and 2620 cases in men, are estimated (31). In Europe, breast cancer remains the most common cancer in females accounting for 28.8% of the total number of cancer diagnosis. The incidence of breast cancer in Europe is more than two times higher than new breast cancer cases in any other region (31, 32). Estimates suggest that approximately 6% of newly diagnosed breast cancer cases present with metastatic disease and that recurrence from early stage to distant sites occurs in 20%-50% of cases (33, 34). The median age of women at the time of breast cancer diagnosis is 62 years; 95% of new cases occur in women aged 40 years or older (35, 36, 18, 19). Recent scientific advances have established hormone-receptor (HR) status and HER2 status as important predictive markers for disease progression and treatment effectiveness. In a registry that included 57 483 case patients, a total of 72.7% of patients were HR(+)/HER2(-), 14.9% were HER2(+) and 12.4% were triple-negative, meaning negative for three receptor types: ER, PgR, and HER2 (19).

2.2.1 Adjuvant hormonal therapy

Adjuvant endocrine therapy significantly improves long-term survival of HR+/HER2- breast cancer patients (20, 37). Patients with invasive breast cancers that are ER and/or PR + should be considered for adjuvant hormonal therapy (HT) regardless of patient age, lymph node status, or whether adjuvant chemotherapy is to be administered (20, 37) and regardless of HER2 status, unless clinically contraindicated. Despite the proven clinical efficacy of tamoxifen or AIs, many breast cancer survivors have recurrence either because of resistance to therapy, non-adherence to treatment, or premature discontinuation of therapy.

In addition, many breast cancer survivors either fail to take the correct dosage at the prescribed frequency or discontinue therapy for tolerance (21).

The adjuvant endocrine treatments are usually given for the standard duration of 5 years. Nevertheless, the high number of recurrences occurring after 5 years suggested that extending adjuvant endocrine therapy beyond 5 years could further improve outcomes, leading to the conduct of several randomized clinical trials. The extended duration of tamoxifen therapy has been shown to improve DFS and overall survival in the ATLAS (38) and aTTom trials (39). Meanwhile, in postmenopausal women, AIs have been shown to be more effective when

compared with tamoxifen. Recently, the DATA (40), IDEAL (41), and NSABP B42 (42) trials showed that extended adjuvant endocrine therapy with AIs beyond 5 years in postmenopausal women with early breast cancer may reduce the occurrence of second breast tumors. However, data from some of these studies (DATA, IDEAL) and others (ABCSG-16) (43) failed to demonstrate a significant benefit of 10 as compared to 7 years of adjuvant endocrine therapy. Furthermore, acute toxicities associated with adjuvant AIs are known to contribute to decreased compliance and also maybe associated with long-term toxicities. Therefore, it is suggested to extend adjuvant treatment only in women with high-risk early breast cancer who tolerate treatment well (44, 45).

2.2.2 Early discontinuation and non-adherence to hormonal therapy

Despite the benefit of adjuvant hormonal therapy (HT) on mortality among women with breast cancer, many women are non-adherent with its use. Hershman et al. investigated the effects of early discontinuation and nonadherence to HT on mortality in women enrolled in Kaiser Permanente of Northern California (KPNC) (1, 11). They identified women diagnosed with hormone-sensitive Stage I–III breast cancer between 1996–2007 and used automated pharmacy records to identify prescriptions and dates of refill. They categorized patients as having discontinued HT early if 180 days elapsed from the prior prescription. For those who continued, they categorized patients as adherent if the medication possession ratio was ≥80%. They used Cox proportional hazards models to estimate the association between discontinuation and non-adherence with all-cause mortality. Among 8769 women who filled at least one prescription, 3802 (43%) received only tamoxifen, while 2313 (29%) received only an AI, and 2654 (30%) received both types of medication. A total of 2761 (32%) discontinued therapy during a median follow-up of 4.5 years: 22% discontinued after AI therapy the first year of treatment. Estimated survival at 10 years was 80.7% for women who continued HT versus 73.6% for those who discontinued (p= <0.001). Both early discontinuation and non-adherence to HT were common and associated with increased mortality (1, 11). Currently, the predictors of treatment discontinuation are not clearly defined. Data from the open label, multicenter, randomized ELPh trial showed that 32.4% of the patients treated with AI discontinued the treatment within 2 years because of adverse effects; 24.3% discontinued specifically because of musculoskeletal symptoms. The median time to treatment discontinuation as a result of any symptom was 6.1 months (range, 0.1 to 21.2 months) and the rate of discontinuation within the first year (excluding relapses) was approximately 20%.

The remaining therapeutic options after early discontinuation of an adjuvant AI due to treatment-related toxicities, are either treatment with another AI or tamoxifen. Many patients do not tolerate transition to a different AI and the last option is therefore either tamoxifen or absence of adjuvant therapy.

2.2.3 Clinical benefit of aromatase inhibitors as adjuvant treatment

As this particular population, patients who have discontinued adjuvant AI prematurely due to treatment-related toxicity, has never been explored in a prospective clinical trial, the BIG 1-98 study conducted in the adjuvant setting using tamoxifen as a comparative arm was selected as a reference to the present study. The BIG 1-98 study (46) was a randomized, Phase 3, double blind

trial that compared 5 years of treatment with various adjuvant endocrine therapy regimens in postmenopausal women with hormone-receptor–positive breast cancer: letrozole, letrozole followed by tamoxifen, tamoxifen, and tamoxifen followed by letrozole. Of note, patients were enrolled regardless of the HER2 status of the primary tumor. The primary analysis compares the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially; events and follow-up in the sequential-treatment groups were included up to the time that treatments were switched.

A total of 8010 women were enrolled, 4003 in the letrozole group and 4007 in the tamoxifen group. After a median follow-up of 25.8 months, 351 events had occurred in the letrozole group and 428 events in the tamoxifen group, with five-year DFS estimates of 84.0% and 81.4%, respectively. As compared with tamoxifen, letrozole significantly reduced the risk of an event ending a period of disease free survival (DFS) ([HR] 0.81; 95 % CI, 0.70 to 0.93; P = 0.003), especially the risk of distant recurrence (HR=0.73; 95 % CI 0.60 to 0.88; P = 0.001) (46). In addition, at a median follow-up of 71 months after randomization, analyses of sequential treatment arms, letrozole followed by tamoxifen (1540 patients) and tamoxifen followed by letrozole (1548 patients) were performed and compared to letrozole monotherapy arm (1546 patients). The primary endpoint, DFS, was not significantly superior for patients randomized to either sequential treatment as compared with letrozole alone (HR for tamoxifen followed by letrozole, 1.05 (99% [CI], 0.84 to 1.32) and HR for letrozole followed by tamoxifen, 0.96 (99% CI, 0.76 to 1.2). However, there were more early relapses among women who were assigned to tamoxifen followed by letrozole than among those who were assigned to letrozole alone. The updated analysis of monotherapy showed that there was a nonsignificant difference in overall survival between women assigned to treatment with letrozole and those assigned to treatment with tamoxifen (HR for letrozole, 0.87; 95% CI, 0.75 to 1.02; p = 0.08). The rate of AEs was as expected on the basis of previous reports of letrozole and tamoxifen therapy (47). Thromboembolism, endometrial cancer, and vaginal bleeding were more common in the tamoxifen group whilst women in the letrozole group had higher incidences of skeletal events, cardiac events and hypercholesterolemia.

2.2.4 Rationale for the duration of prior anti-aromatase inhibitor therapy

Data from the Oxford individual patient meta-analysis on 31920 postmenopausal women enrolled in nine randomized trials of AIs *versus* tamoxifen were published in 2015 and showed that the benefit of AIs over tamoxifen is accrued in the first two years of the randomized comparison (44).

- In the comparison of 5 years of aromatase inhibitor versus 5 years of tamoxifen (9885 patients), most of the benefit of aromatase inhibitor over tamoxifen was accrued over the first 2 years of treatment with a 36% relative risk (RR) of any disease recurrence during years 0-1 after surgery (RR = 0.64, 0.52-0.78), dropping to 20% during years 2-4 (RR = 0.80, 0.68-0.93). No further significant effect was observed after both treatments are stopped.
- In the other comparison including 11798 patients who were disease-free after 2 years of tamoxifen and then randomized to either continue tamoxifen or to switch to an aromatase inhibitor, allocation to an aromatase inhibitor reduced the recurrence rate during years 2-4 (RR = 0.56, 0.46-0.67) with no significant further effect on recurrence after the treatment

period. These results suggest that most of the benefit of aromatase inhibitor is delivered over the first 2 years of treatment.

Based on the above-mentioned findings, the treatment with AI up to 2.5 years followed by tamoxifen is an effective treatment for patients who have discontinued adjuvant AI therapy due to treatment-related toxicities.

2.2.5 Rationale for the inclusion of participants with HER2+ disease

In the last two decades, improved clinical outcomes were registered for most trials in comparison with older studies as a result of mammography screening and progresses in the management of early-stage breast cancer. This is evident particularly for HER2+ tumors following the introduction of trastuzumab into the therapeutic armamentarium of the metastatic disease starting from early 2000 and then as adjuvant therapy for early-stage disease a few years later.

BIG1-98 study enrolled participants with HR+ disease irrespective of HER2 status between March 1998 and May 2003. At that time trastuzumab was not yet approved for the treatment of HER2+ early-stage breast cancer. Hence, BIG1-98 population is characterized by higher risk profile due to the absence of anti-HER2 treatment in comparison with subsequent trials for HER2+ disease (48).

Participants with histologically confirmed HR+ breast adenocarcinoma are eligible for the AMEERA-6 study, regardless of HER2 status. Those with HER2+ disease can be enrolled provided that they have been treated with chemotherapy and are no longer receiving anti-HER2 systemic adjuvant therapy.

Despite completion of anti-HER2- systemic adjuvant therapy, patients with HR+/HER2+ disease unfortunately remain at risk for disease recurrence. These patients should be treated with endocrine therapy for at least 5 years, and, similar to the participants on AMEERA-6 with HR+/HER2- disease, may also benefit from further adjuvant endocrine therapy in the context of early discontinuation of AI due to treatment-related toxicity.

2.2.6 Rationale for Hormone receptor positivity threshold

Hormone receptor positivity ≥10% is proposed, as per American Society of Clinical Oncology (ASCO)/College of American Pathologist guidelines (49). There are limited data on the overall benefit of endocrine therapies for patients with low level (1-10%) ER expression. Data suggest that invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more like ER-negative cancers.

2.2.7 Rationale for the primary endpoint

IDFS as per STEEP criteria, defined as the time from the date of randomization to the date of the first event of ipsilateral invasive breast tumor recurrence, regional invasive recurrence, distant recurrence, death, contralateral invasive breast cancer, or second non-breast primary invasive cancer, has been widely used as primary endpoint in recent adjuvant breast cancer studies

[monarchE (50), PALLAS (51), EarLEE-2 (52). However, the inclusion of the event of second primary cancer in the IDFS definition was a subject of considerable discussion:

- As noted in Hudis et al, (4) it may be difficult to distinguish a second primary cancer in a nonbreast site (which may or may not be related to the primary cancer) from a distant recurrence of the primary breast cancer especially when the tumor site is not easily accessible for biopsy.
- There is a well-known association between treatment and some second primary cancers. This is the case, for instance, of tamoxifen-induced endometrial cancer. Including events not related to the primary breast cancer or to the administered treatment might eventually dilute the treatment effect. Thus, including most types of second primaries of non-breast origin, except endometrial cancer, may be less relevant to the assessment of the treatment benefit of amcenestrant over tamoxifen in terms of improving breast cancer outcomes.
- In addition, it has been shown in independent cohorts that the rate of second primary invasive cancers of nonbreast origin is increasing with age (53, 54). Considering that recent clinical trials enrolled older patients, the risk of second primary invasive cancers that might not be related to the primary breast cancer or to the treatment of the study population is not negligible.

Based on these considerations, we have opted for IBCFS as the primary endpoint, excluding the second non-breast primary invasive cancers as event of interest. Our primary endpoint selection was also based:

- on the use of IBCFS as the primary endpoint in other Phase 3 trials conducted in patients diagnosed with HER2-positive early breast cancer (54, 55).
- on the recent revision of the STEEP criteria in adjuvant breast cancer by an international group of academic breast oncologists, as well as representatives from ASCO, the US National Cancer Institute (NCI), and the US Food and Drug Administration (FDA) (3). In this second version of the STEEP criteria, authors ultimately recommend the use of an additional endpoint, invasive breast cancer-free survival (IBCFS) which includes all IDFS events except second non-breast primary invasive cancers.

2.2.8 Rationale for the assumption in the tamoxifen arm

The intention of AMEERA-6 trial is to determine whether amcenestrant compared with tamoxifen improves IBCFS in patients who discontinued prior AI due to treatment-related toxicities. For the purpose of this study, patients diagnosed with early-stage breast cancer who are at high risk of disease recurrence will be selected.

Regarding justification and rationale for the statistical assumption of the performance of participants treated on the tamoxifen arm in AMEERA-6, namely 4-year IBCFS of 82%, data from historical as well as more contemporaneous studies is informative.

In the BIG 1-98 study (46), wherein the high-risk population represented 41% of the global trial population, the 5-year DFS among patients with node positive cancer was 77.9% in the letrozole-only group in comparison with 71.4% in the tamoxifen-only group.

Meanwhile, more recent adjuvant trials in patients with ER+/HER2- early breast cancer evaluated the combination of CDK4/6-inhibitors with endocrine therapy as compared to standard endocrine therapies.

In the PALLAS study, eligible patients were randomly assigned to receive palbociclib for 2 years plus endocrine therapy or standard endocrine therapy with or without an LHRH agonist. Primary endpoint was IDFS using STEEP definition and IBCFS was defined as a correlative and exploratory endpoint. Adjuvant endocrine therapy selection included 3872 (67.2%) of 5760 patients initiating an AI, 1872 (32.5%) patients initiating tamoxifen, and 1136 (19.7%) patients receiving a concurrent LHRH agonist, similarly in both treatment arms. Among the 5760 randomized patients, 3382 (58.7%) had high clinical risk, defined as more than 4 positive nodes, or one to three positive nodes either T3 or T4, or Grade 3 disease, or both. Results of the second interim analyses were reported recently. Invasive DFS did not statistically differ between the two groups, with a 3-year IDFS of 88.2% (95% CI 85.2-90.6) in the palbociclib plus endocrine therapy group, and 88.5% (85.8-90.7) in the endocrine therapy alone group (HR 0.93 [95% CI 0.76-1.15]; logrank p = 0.51). When considering the exploratory endpoint of IBCFS, the 3-year IBCFS rate was 89.5% (95% CI 86.9-91.7) in the endocrine therapy alone group. In the high-risk clinical group, the 3-year IDFS rate was 83.6% (95% CI 78.7-87.7) in the endocrine therapy alone group (51).

In the monarchE study, eligible patients were randomly assigned to receive abemaciclib for 2 years plus endocrine therapy or standard endocrine therapy. Patients were eligible if they were at high risk of recurrence, defined as more than 4 positive nodes or one to three positive lymph nodes and at least one of the following features: tumor size ≥5 cm, histologic Grade 3, or centrally assessed Ki-67 ≥20%. Primary endpoint was IDFS using STEEP definition. The second interim analysis was reported at a median follow-up of 15.5 months. Anti-aromatase inhibitor was prescribed as the first endocrine therapy in 68.3% and tamoxifen in 31.4% patients randomized to the control arm. At the time of analysis, abemaciclib plus endocrine therapy demonstrated a statistically significant improvement in IDFS versus ET alone (HR, 0.75; 95% CI, 0.60 to 0.93), with 2-year IDFS rates of 92.2% in the abemaciclib arm versus 88.7% in the control arm (50).

Other relevant historical studies have reported results in patients treated with a switch strategy with sequential adjuvant endocrine therapy after a period of being disease-free.

The Intergroup Exemestane Study (IES) randomized postmenopausal women with ER+/unknown primary invasive breast cancer who remained disease free after 2 to 3 years of tamoxifen to either tamoxifen or exemestane for the remainder of the 5-year endocrine therapy period. Although this study assessed the other sequence of endocrine therapies as compared to the AMEERA-6 study (tamoxifen then anti-aromatase inhibitor versus continued tamoxifen) and the patient population which will be enrolled in AMEERA-6 is at higher risk of recurrence, these results can provide useful insights on clinical outcomes achieved after a period of being disease-free. At a median follow-up of 120 months, the cumulative incidence of breast cancer events remains constant for many years (56). A similar pattern of recurrence risk has been observed in a comparison from the Oxford meta-analysis including 11798 patients who were disease-free after 2 years of tamoxifen and then randomized to either continue tamoxifen or to switch to an aromatase inhibitor (53).

In this patient population, risk of disease recurrence is expected to remain similar over time as suggested by the Oxford meta-analysis and individual clinical trials evaluating adjuvant endocrine therapies, around 4 to 5% per year considering events qualifying for IBCFS endpoint.

In summary, data from these studies is considered supportive for the reference value of 4-year IBCFS of 82% is considered for the control arm of AMEERA-6.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of amcenestrant may be found in the IB.

Based on amcenestrant experience and the observed safety profile in the ongoing studies, as well as on safety precautions that have been established to safeguard the wellbeing of the participants, the benefit-to-risk assessment is deemed acceptable within the context of the planned AMEERA-6 study.

Moreover, the clinical benefit is expected to be relevant in patients, as preclinical findings and clinical pharmacodynamic results show a very high saturation of the ER at the tumor level. This current comparative study aims to show a relevant improvement of the efficacy of amcenestrant versus tamoxifen.

2.3.1 Risk assessment

To date, the efficacy and safety data from ongoing studies of amcenestrant support continued clinical development of amcenestrant. Based on non-clinical toxicity study results, completed or ongoing clinical studies in patients and in healthy post-menopausal participants, there have been no important identified risks confirmed so far. The important potential risks as per non-clinical toxicity and in vitro assessments include the following: gastrointestinal (GI) toxicity and complications; hepatotoxicity; photosensitivity; drug-drug Interaction; rash; osteoporosis and fertility impairment. Routine Pharmacovigilance (PV) activities are being conducted to monitor these potential risks associated with amcenestrant. Potential risks are summarized in Table 1.

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention Amcenestrant (SAR439859)		
Gastrointestinal toxicity	AMEERA-1 Arm#1 (Parts A and B): A total of 22 out of 62 patients who received amcenestrant monotherapy (>20 mg QD) developed various GI toxicities considered to be related to amcenestrant, none of them were of Grade ≥3. AMEERA-1 Arm#2 (Parts C and D): A total of 19 out of 39 patients who received 200 mg amcenestrant and palbociclib developed GI toxicities considered to be associated to amcenestrant, none of them were of Grade ≥3. In studies conducted in healthy subjects, there were few single occurrences of GI events considered related to amcenestrant. None of them were of Grade ≥3	Events ≥ Grade 3 are to be closely monitored. Preventive or corrective treatment(s): antiemetics, antidiarrheal.
Hepatotoxicity	Preclinical safety data have shown evidence of hepatotoxicity in repeat dose toxicity study at 100 mg/kg/day in dogs. AMEERA-1 Arm#1 (Parts A and B) / Arm#2 (Parts C and D): No event of hepatotoxicity considered to be related to amcenestrant has been reported. Studies in healthy subjects: In completed or ongoing studies in healthy subjects, 3 subjects developed asymptomatic transient ALT increase ≥ 2 × ULN with amcenestrant 300 mg SD alone or in combination with rifampicin. All occurrences were Grade 1. All events of ALT increase were non serious and spontaneously resolutive.	Monitor LFT in cases of increase of Grade≥3 ALT, listed as AESI in the study. Monitor patients with symptoms/signs suggestive of hepatotoxicity: jaundice, increase of liver function tests (LFT) (ALT, AST, GGT, ALP and bilirubin). Patients with impaired liver function should not be included in the study (exclusion criterion E 20).
Phototoxicity	A phototoxicity risk for amcenestrant was identified based on the absorption spectrum of the compound and in an in vitro phototoxicity study in 3T3 cells which was confirmed in a repeat dose in vivo mouse phototoxicity study. Within the amcenestrant development program which includes the sun protection measures, cumulatively Grade 1 sunburns were observed only in 2 patients out of an estimated 700 participants exposed so far to amcenestrant doses (from 20 to 1200 mg). The first patient received amcenestrant 150 mg QD and experienced G1 sunburn while being exposed to sun without sun protection and the second patient developed G1 sunburn after amcenestrant 400 mg QD.	Limitation of exposure to sunlight or artificial sunlight is recommended along with the requirement for sun protection measures (wear protective clothing, use a broad-spectrum sunscreen to cover ultra-violet A (UVA) and ultra-violet B (UVB) light exposure when outdoors with frequent re-application as necessary, along with lip balm (sun protection factor [SPF] ≥30).
Rash	In Ameera 2, 1 Grade 2 rash and 1 serious Grade 3 rash maculo-papular were reported in Japanese patients (respectively at 400 mg QD and 300 mg BID). The last event was declared as a DLT. Grade 1 rashes have been reported in global population.	Closely monitor if further risk mitigation/management is required

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Osteoporosis	Due to mechanism of action of amcenestrant, there is a theoretical risk of osteoporosis when patients are exposed long-term to amcenestrant. No case of osteoporosis has been reported in amcenestrant program. No long-term observation has been performed.	Monitor DEXA at baseline and follow up every 2 years. Monitor bone markers CTX and P1NP at baseline and every 2 years.
DDI	Amcenestrant effect on other drugs: Amcenestrant is • A moderate inducer of CYP3A based on a midazolam clinical study. • A potential CYP2B6, CYP2Cs and UGTs inducer • A potential inhibitor of OATP1B1/1B3 transporters Effect of other drugs on amcenestrant: • In vitro amcenestrant biotransformation occurs mainly through non-CYP enzymes (around 80% of hepatic clearance) involving UGT1A1 and 1A4. CYP2C8 and CYP3A are involved to less than 20%. CYP3A clearance was confirmed to be minimal based on an itraconazole interaction clinical study. • Strong metabolism enzyme inducers (Rifampicin) decrease amcenestrant exposure by 30% No adverse event related to DDI has been reported in clinical studies as of 29 May 2021.	Drugs which are sensitive substrates of CYP3A, CYP2B6, CYP2Cs, and/or UGT should be closely monitored for efficacy. Treatment with drugs that are sensitive substrates of OATP1B1/1B3 (asunaprevir, batorvastatin, bosentan, danoprevir, fexofenadine, glyburide, nateglinide, pitavastatin, pravastatin, repaglinide, rosuvastatin and simvastatin acid) should not be administered with amcenestrant. Drugs that are UGT inhibitors (ie, probenecid, atazanavir) should not be administered with amcenestrant. Drugs that are strong inducers of CYP3A should not be administered with amcenestrant. Patients with concomitant medications that are considered to interact with amcenestrant should be excluded (exclusion criteria: E 12, E 13, E 14, E 15 and E 16).
Study procedures		
Mammography	Mammography to be performed annually with the risk of irradiation inducing potential cancers. However, this risk is considered minimal due to the low level of radiation. In addition, this procedure is standard for monitoring patients in the adjuvant setting.	None
Biopsies	It is normal practice to biopsy possible recurrence of breast cancer to (a) confirm diagnosis and (b) check for change of subtype.	When required, biopsies should be done only when tumor is accessible, limiting the risk of Infection or bleeding at the biopsy site. Special caution is needed for patients on anticoagulants, with INR increased, or with thrombocytopenia.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Other: Study intervention Tamoxifen		
Uterine malignancies	An increased incidence of uterine malignancies (endometrial adenocarcinoma and uterine sarcoma), including fatal cases, has been reported with tamoxifen treatment.	Promptly evaluate abnormal vaginal bleeding in woman with current or past tamoxifen use. Patients receiving or who have previously received tamoxifen should have annual gynecological examinations. Advise patients to promptly inform healthcare providers if they experience any abnormal gynecological symptoms (eg, menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge, or pelvic pain or pressure).
Thromboembolic events	There is an increased incidence of thromboembolic events, including DVT and pulmonary embolism, during tamoxifen therapy.	Carefully consider the risks and benefits of tamoxifen in women with a history of thromboembolic events. Advise patients to seek medical attention immediately if signs or symptoms of a thromboembolic event occur. Participants with abnormal coagulation profiles, or any history of coagulopathy within 6 months prior to the first dose of IMP including history of DVT or pulmonary embolism should be excluded (exclusion criterion: E 07.
Hepatotoxicity	Tamoxifen has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis, and hepatic necrosis. Some of these serious cases included fatalities. In most reported cases, the relationship to tamoxifen is uncertain. However, some positive rechallenges and dechallenges have been reported. Liver cancer and liver abnormalities, some fatal, have occurred.	Perform periodic liver function testing as indicated in the protocol (as mentioned above for amcenestrant).
Eye disorder	There is a risk of ocular disorders with the use of Tamoxifen. Adverse drug reactions (ADR) have been reported in large Phase III clinical studies. The study treatment should be permanently discontinued in case of first recurrence of the same Grade 4 event considered related to the IMPs even though few Grade ≥3 adverse event are expected.	Monitor ocular disorders as part of side effects related to Tamoxifen. Ensure appropriate surveillance and prompt evaluation of visual complaints.
Embryo-fetal toxicity	Can cause fetal harm.	Advise females of reproductive potential and male with partner of reproductive potential of the potential risk to a fetus and to use effective contraception as indicated in the protocol.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
DDI	Concomitant medications with drugs that inhibit CYP2D6 may lead to reduced concentrations of the active metabolite endoxifen, one of the most important active metabolites of tamoxifen. This could lead to reduced efficacy of tamoxifen. A marked increase in anticoagulant effect may occur when tamoxifen is used in combination with warfarin. Strong CYP3A inducers (eg, rifampin) reduce tamoxifen exposure.	Strong inhibitors of CYP2D6 (eg, paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should be avoided during the study. When warfarin is prescribed, closely monitor coagulation indices for increased anticoagulant effect in patients. Strong CYP3A inducers should not be used with tamoxifen (as mentioned above for amcenestrant).

2.3.2 Benefit assessment

This new generation SERD, with an expected almost full inhibition of the ER target may represent a new therapeutic option with a better benefit/risk ratio than approved endocrine monotherapies, such as AIs, tamoxifen, and fulvestrant.

Amcenestrant could provide meaningful benefit to participants who have a high-risk breast cancer disease and limited options after early discontinuation of AI adjuvant due to treatment-related toxicities. Moreover, preclinical findings and clinical pharmacodynamics show a very high saturation of the ER at the tumor level. This current comparative study aims to show a relevant improvement of the efficacy of amcenestrant versus tamoxifen.

2.3.3 Overall benefit: risk conclusion

Based on amcenestrant experience and the observed safety profile in the ongoing AMEERA-1 study, as well as on safety precautions that have been established to safeguard the wellbeing of the participants, the benefit-to-risk assessment is deemed acceptable within the context of the planned AMEERA-6 study.

Considering the measures taken to minimize risk to participants, the potential risks identified in association with amcenestrant are justified by the anticipated benefits that may be afforded to the study participants who have a high-risk breast cancer disease and limited options after AI adjuvant treatment discontinuation due to treatment-related toxicities.

2.3.4 COVID-19 risk and benefit assessment

Cancer patients are at increased risk of contracting SARS-CoV-2 infection and running more severe disease course (57). Cancer encompasses a heterogeneous group of subtypes and stages and the patient's risk profile should therefore be individualized taking into consideration primary tumor type and stage as well as age and sex. The benefit and risk balance of anti-tumor treatments should be also tailored considering the overall treatment goal. For cancer in the curative setting, this risk/benefit balance favors maintaining systemic treatments. Based on a recently published consensus statement, some systemic therapies for the adjuvant treatment of early breast cancer, ie, endocrine therapy, are in principle not associated with risk of complications of COVID-19 and

should therefore be used as recommended by the guidelines (58). In the context of the AMEERA-6 trial, no study-related risk minimization measures are recommended based on the favorable risk/ benefit balance of study population and anti-cancer treatment. The investigators should always exercise their medical judgement to individualize clinical decisions and adhere to local and institutional guidelines for SARS-CoV-2 infection prevention and vaccine administration.

Refer to the contingency measures for a regional or national emergency that is declared by a governmental agency detailed in Section 10.9, (Appendix 9).

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 - Objectives and endpoints

Objectives	Endpoints
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	• IBCFS is defined according to Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP) criteria version 2.0 (3) 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 endpoint**	
• 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	• IDFS is defined according to STEEP criteria (4) 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

Objectives	Endpoints
Other secondary endpoints	
• To evaluate the distant recurrence-free survival (DRFS) in both treatment arms	• DRFS is defined according to STEEP criteria (4) 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).
• To evaluate the locoregional recurrences-free survival (LRRFS) in both treatment arms	• 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).
• To evaluate the overall survival (OS) in both treatment arms	• OS is defined as the time interval from the date of randomization to the date of death due to any cause.
• To evaluate the breast cancer-specific survival (BCSS) in both treatment arms	• BCSS is defined as the time interval from the date of randomization to the date of death attributable to breast cancer cause
• To evaluate patient-reported overall treatment-related side effect bother, treatment-related symptoms, and quality of life in both treatment arms	• 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
• To evaluate safety in both treatment arms	• Adverse events (AEs)/serious adverse events (SAEs), laboratory abnormalities and adverse events of special interest (AESIs).
• To characterize the pharmacokinetics (PK) of amcenestrant	• Amcenestrant predose concentrations

Objectives	Endpoints
Tertiary	
• To perform exploratory analyses of tumor tissue samples to investigate the predictive and prognostic value of sensitivity to endocrine therapy assessed by SET2,3 index measurement	• Relationship between SETER/PR and SET2,3 index measurements assessed using FFPE slides and efficacy endpoints
• To perform exploratory analyses of tumor tissue, serum, and plasma samples before treatment initiation to investigate the predictive and prognostic value of novel biomarkers related to safety and efficacy endpoints	• Relationship between tumor derived tumor makers (DNA- or RNA-based and protein markers) before treatment initiation and safety / efficacy endpoint
• To perform exploratory analyses of tumor tissue, serum, and plasma samples before treatment initiation to investigate the predictive and prognostic value of novel biomarkers related to safety and efficacy endpoints	• Relationship between the changes from baseline and corresponding distribution of tumor derived tumor makers (DNA- or RNA-based and protein markers) upon disease recurrence and efficacy endpoints
• To perform exploratory analyses of circulating tumor DNA to investigate the predictive and prognostic value of ESR1 mutation	• Relationship between ESR1 mutations assessed in the ctDNA from plasma samples collected throughout the study and efficacy endpoints
• To perform exploratory analyses of tumor tissue samples to investigate the predictive and prognostic value of breast cancer molecular subtypes (eg, Luminal A, Luminal B, non-Luminal)	• Relationship between genomic signatures assessed using RNA sequencing data and efficacy endpoints
• To perform exploratory analyses of tumor tissue samples to investigate the predictive and prognostic value of histological type (ductal, lobular, others)	• Relationship between histological type and efficacy endpoints
• To perform exploratory analyses aimed at identifying biomarkers are associated with resistance to endocrine therapy	• Relationship between biomarkers collected throughout the study and efficacy endpoints. Biomarkers include tests performed in blood and tumor tissue, including, but not limited to the following: - ctDNA mutations analysis. - breast cancer molecular subtypes assessed using RNA sequencing. - ER activation score by RNA sequencing. - ER, PgR, Ki67, and Bcl-2 protein expression assessed using immunohistochemistry (IHC).
• To evaluate patient-reported functional impact, treatment- related symptoms, health state utilities, and adherence in both treatment arms	• This PRO objective will be assessed by the following endpoints: - Change from baseline in physical functioning as measured by the 5-item physical functioning scale of the EORTC-QLQ-C30. - Change from baseline in physical functioning as measured by the 8-item EORTC short form physical functioning scale (which includes physical function items from the EORTC QLQ-C30 and EORTC IL127). - Patient-reported treatment-related symptoms will be measured using PRO-CTCAE items.

Objectives	Endpoints
	- Health state utilities will be measured with the EQ-5D-5L. - Patient-reported medication adherence will be measured with the 8-item Morisky Medication Adherence Scale (MMAS-8). - Patient global impression of change (PGIC) in side effects of treatment and patient global impression of severity (PGIS) in side effects of treatment will be measured by PGIC and PGIS items.

For China, please see Section 10.8 for details.

3.1 APPROPRIATENESS OF MEASUREMENTS

The rationale for the choice of IBCFS as the primary endpoint has been extensively discussed in the Section 2.2.7 to be a more precise breast-cancer specific outcomes in this setting. IDFS has been widely used in other studies in the adjuvant setting and is considered as a key secondary endpoint in this study. Its formal testing will be performed if the primary test on IBCFS is significant and a particular care will be given to the description of the event contributing to this endpoint. Efficacy endpoints were defined as per the STEEP standardized definitions for efficacy endpoints in adjuvant breast cancer clinical trials (4) and its recent update STEEP Version 2.0 (3). The secondary efficacy endpoint LRRFS was defined using the definition in the recent previous trial conducted in this setting (50, 51), including the invasive contralateral breast cancers in the event definition.

The current study will enroll a patient population who did not tolerate aromatase inhibitors; therefore, the evaluation of patient-reported outcomes is of importance including overall-treatment related side effect both, treatment-related symptoms, and functional impact on quality of life. Self-reported treatment adherence is also of interest. All PRO questionnaires used in this study are validated questionnaires as described in Section 8.10.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is 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 will have 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 have discontinued adjuvant AI therapy due to treatment-related toxicity will enter the screening period to assess their eligibility.

Participants still on AI treatment may enter the screening period for central confirmation of biomarkers and screening imaging assessments. The other assessments/questionnaires required before randomization will be performed/completed when patient is off the AI therapy.

All eligible participants for whom ER and PgR status have been centrally confirmed will be 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 will also receive the matching placebo of the other treatment under evaluation. Both treatments are given orally.

The study population will be 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 will be 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

During the treatment period, men and pre/perimenopausal women will receive GnRH analogs as approved in the respective countries.

Participants will receive their assigned treatment for the planned duration of 5 calendar years or until diagnosis of disease recurrence per IBCFS definition or any other withdrawal criterion whichever occurs first.

Early discontinuation during the active study treatment period will be left at the investigator's discretion.

Extended adjuvant endocrine therapy upon completion of study treatment is allowed, but treatment will not be provided by the sponsor. Treatment recommendation should be considered on an individual patient basis taking into consideration clinico-pathologic characteristics, patient's preferences, and total duration of adjuvant endocrine therapy at the time of study treatment completion or discontinuation. When extended adjuvant endocrine therapy is considered, treatment options include adjuvant tamoxifen or adjuvant aromatase inhibitor.

In case of diagnosis of second non-breast primary invasive cancers, the decision to keep the patient on protocol treatment is based on clinical judgement of the treating physician. Patients diagnosed with a second primary malignancy not requiring systemic therapy (ie, chemotherapy, hormonal therapy, targeted therapy, etc) and with no evidence of breast cancer recurrence may continue with study drug treatment according to the protocol and schedule of assessment, if considered by the investigator to be in the patient's best interest, whenever possible. Study treatment may be temporarily suspended to allow for local treatment (surgery and/or radiation) of the second non-breast primary invasive cancer; in this situation, the maximally allowed period of protocol treatment discontinuation should not exceed a total of 3 months in any 12-month time period.

Participants discontinuing or completing the active study treatment period will be followed up to 10 years from randomization, except in case of premature study termination due to one of the following reasons: withdrawal of consent, loss to follow-up or death.

An IDMC will monitor the safety data on a periodic basis. The IDMC will make recommendations as to whether the trial should continue based on ongoing reviews of safety data. The IDMC will also evaluate efficacy at the interim analyses and make a recommendation regarding study continuation based on observed results of the current study and/or external study data generated with amcenestrant. The IDMC procedures will be described in the full protocol and detailed in the IDMC charter and will be approved by IDMC members.

A Study Steering Committee will supervise the progress of the trial, review relevant information that may affect the study conduct as well as review and take decisions to act on the IDMC recommendations.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The purpose of the proposed study is to demonstrate the superiority of amcenestrant *versus* tamoxifen with regard to IBCFS in patients with HR+ early breast cancer who have discontinued AI as adjuvant treatment due to treatment-related toxicities. For this population, there are currently limited treatment options after AI discontinuation, including switching to another AI which may have similar side effects, or switching to tamoxifen.

This is a randomized double-blinded placebo-controlled clinical trial, which is a gold standard to be able to change the current treatment guidelines.

The scientific rationale for key aspects of the study design including patient population, choice of the primary endpoint have been detailed in the Section 2.1 and Section 2.2 .

4.2.1 Participant input into design

During the development of the study concept, the sponsor conducted patient panels and interviews with 40 participants (representing 5 countries in 3 regions) in April and May 2020. The patients supported the development of an adjuvant endocrine therapy with an improved safety profile and less side effects as well as innovative methods using technology to reduce the burden of clinical trial participation.

During the development of the AMEERA-6 study, 9 patient representatives from the BIG's Patient Partnership Initiative (PPI) were involved in the assessment of the PRO scales and adherence questionnaires to be implemented in the study.

In particular, after having familiarized with the rationale behind the study and its proposed design, the patient partners were asked to provide their feedback on the 8 health-related quality of life (HRQL) scales and 2 adherence questionnaires that were proposed by a group of **experts in the field, in particular on the following aspects:**

1. Burden and frequency of **the questionnaires**
2. Satisfaction on the way the selected tools capture the discomfort that can occur with endocrine treatment
3. Intrusiveness of **the questions and scales**
4. **Non-adherence scale**
5. Format of the questionnaires (digital versus **paper-based**)

Based upon the feedback received from the patient representatives, three major changes were implemented in the protocol:

- The breast version of the MIS-A questionnaire assessing adherence to treatment was removed. This topic will be assessed by the Morisky Medication Adherence Scale (MMAS-8) questionnaire.
- Baseline PRO assessment: Originally, two baseline assessments were foreseen, one before randomization (ie, screening period) and at treatment start (D1C1). Given the remark of the PPI group that the intensity of the assessment was too high, it was decided to perform only one PRO assessment on D1C1 or earlier if patient has no unrecovered acute toxic effects of prior AI therapy.
- Late follow-up: The patient representatives' review indicated there was interest in a long-term follow-up, given the good prognosis of these patients. Therefore, the protocol was updated with an additional post-treatment follow-up visit at two years after treatment.

4.3 JUSTIFICATION FOR DOSE

The term “dose” refers to 200 mg orally once daily for amcenestrant and to 20 mg orally once daily for tamoxifen.

A dedicated window-of-opportunity AMEERA-4 (ACT16106) study with amcenestrant in pre-operative ER+/HER2- postmenopausal breast cancer patients is currently ongoing. Findings from the administrative interim analysis of AMEERA-4 undertaken in April 2021 following the randomization of the first 63 patients have been used to support the dose of amcenestrant used in this study (Section 2.1.2). While the pharmacodynamic activity and safety results from AMEERA-4 could support use of either amcenestrant 200 mg or 400 mg in the AMEERA-6 study, the lower dose of 200 mg is preferred given the proposed long-term exposure (5 years) in early breast cancer, in particular for these study participants who discontinued prior adjuvant AI due to treatment-related toxicities.

The regulatory approved and administered schedule of tamoxifen 20 mg orally daily in adjuvant breast cancer will be used in this study.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study. Participants completing the active 5-year study treatment period or discontinuing prematurely will be followed up for 10 years from randomization. A participant is considered to have completed the study if he/she has completed all phases of the study including 5 years of treatment period and 5 years of post-treatment period for the follow-up, except in case of premature study termination due to one of the following reasons: withdrawal of consent, loss to follow-up or death.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be 18 years of age inclusive or older, or country's legal age of majority if the legal adult age is >18 years old, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with histologically confirmed diagnosis of adenocarcinoma of the breast with documentation of ER+ (≥10% positive stained cells) and/or PgR+ (≥10% positive stained cells) based on invasive breast tumor cell staining by immunohistochemistry (IHC) assay consistent with central assessment. If axillary lymph nodes are tested, ER and/or PgR must also be positive.

- Participants with bilateral invasive disease are allowed only if the contralateral breast tumor meet the criteria regarding ER and PgR-status described above.
- In case of multicentric or multifocal or synchronous bilateral breast cancer, the lesion considered at highest risk for recurrence based on the investigators' discretion will be used for central pathology review and stratification.

I 03. Participants irrespective of HER-2 status (HER2-positive, HER2-negative, unknown) as assessed per ASCO/College of American Pathologist guidelines (59), are eligible provided in each case they meet the ER and PgR criteria in I 02.

- HER2-negative is defined as a score of 0, 1+ by IHC or a negative in situ hybridization (ISH) based on single-probe average HER2 copy number
- HER2-positive is defined as a score of 3+ by IHC or a positive ISH based on single-probe average HER2 copy number. All adjuvant anti-HER2 treatment and chemotherapy must be completed prior to randomization.

I 04. Participants with Stage IIB or Stage III invasive breast cancer per the AJCC Cancer Anatomic Staging 8th edition who have undergone adequate (definitive) breast surgery and adjuvant radiation (if indicated) for the current malignancy. Participants with inflammatory breast cancer are not eligible.

- In participants having received upfront surgery with or without adjuvant systemic therapy, eligibility is based on pathological staging (pTNM) rather than clinical staging (cTNM), in case there is a discordancy between these.

- If neoadjuvant systemic therapy was administered, participants must have Stage IIB or Stage III invasive breast cancer based on clinical staging (cTNM) and have residual nodal disease after definitive breast surgery (ypN1-3).
    - Participants with only residual micrometastatic disease (N1mic) or isolated tumor cells (ITCs) in the axillary lymph nodes are not eligible.

NOTE: the One-Step Nucleic Acid Amplification (OSNA) method is acceptable for sentinel lymph-node assessment.

I 05. Participants who have received prior AIs (letrozole, anastrozole or exemestane or any sequence thereof) per the following:

- Adjuvant AI therapy was discontinued due to treatment-related toxicity.
- Minimum of 6 months duration of AI therapy is required
- Maximum of 30 months duration of AI therapy is required (from initiation of first AI if there was a switch between AIs)
- AIs are permitted in neoadjuvant setting and count toward the 30-month maximum duration. However, a minimum of 3 months of AI therapy are required in the adjuvant setting.

NOTE:

- *A patient will not be eligible if he/she received AIs in only the neoadjuvant setting (at least 3 months of adjuvant AI therapy is required),*
- *Switch between different adjuvant AIs before discontinuation is allowed.*

I 06. Participants for who the last AI adjuvant therapy was discontinued less than 3 months prior to randomization but stopped at least 1 week prior to patient randomization onto the trial.

NOTE: *In this case, the tumor material and imaging work up can be performed while participants are still treated with AIs. The other assessments/questionnaires required before randomization will be performed/completed when patient is off the AI therapy.*

I 07. Prior systemic therapies other than AI(s):

- Participants who received prior treatment with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are allowed but treatment must have a wash-out period of at least 4 weeks between the last dose of the CDK4/6 inhibitor and randomization onto the trial.
- Participants who received prior treatment with Poly ADP ribose polymerase (PARP) inhibitors or other oral anticancer agents (including oral fluoropyrimidines such as S-1 and capecitabine) are allowed but must have a wash-out period of at least 2 weeks between the last dose of the anticancer agent and randomization.

I 08. Participants with absence of locoregional and/or advanced/metastatic disease with following imaging test(s):

- A negative bilateral mammogram at study entry is required (exam does not need to be repeated if performed within 6 months prior to randomization). In participants with prior mastectomy, unilateral mammogram will be performed. In participants with prior bilateral mastectomy, mammogram is not indicated.

NOTE: *if local investigator plans to use MRIs instead of mammograms during the study, MRI will have to be performed at baseline.*

- Baseline staging must be performed prior to study enrollment for the following participants:
  - Participants with symptoms suggestive of metastatic disease indicated per investigator's judgment (for example, if patient is symptomatic for bone pain and/or if alkaline phosphatase is significantly elevated ≥ 3×ULN).
  - Participants diagnosed with stage IIIA or higher and no staging evaluation was performed prior to study enrollment. Staging must include chest, abdominal ± pelvic, and bone imaging and clinical evaluation of superficial disease. Examination type for staging can include sonography, bone scan, CT, MRI and/or PET-CT as per investigator's choice.

I 09. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1.

I 10. Willingness and ability to provide tumor tissues (ie, archived formalin fixed paraffin embedded [FFPE] tissues).

Weight

Not applicable.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 11. All

For the contraceptive and barrier guidance, please refer to Appendix 4 Section 10.4. Contraceptive use by men with a partner of childbearing potential or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

- Male with no prior bilateral orchiectomy can be enrolled if amenable to be treated with goserelin or other GnRH analog approved for use in early breast cancer in the respective countries.

b) Female participants

- Postmenopausal women as defined by one of the following:
  - Age ≥60 years
  - Age <60 years:
    a) With spontaneous cessation of menses >12 months prior to randomization in the absence of chemotherapy, tamoxifen and toremifene.
    b) Or with cessation of menses of duration ≤12 months or secondary to hysterectomy AND have follicle stimulating hormone (FSH) and estradiol level in the postmenopausal range according to institutional standards (or >34.4 IU/L for FSH and <10 pg/mL for estradiol if institutional range is not available) prior to randomization,
    c) Or who have received hormonal replacement therapy but have discontinued this treatment AND have FSH and estradiol level in the postmenopausal range according to institutional standards (or >34.4 IU/L for FSH and <10 pg/mL for estradiol if institutional range is not available) prior to randomization,
    d) Or with status post bilateral surgical oophorectomy,
    e) Or post bilateral ovarian ablation through pelvic radiotherapy: recommended to have FSH and estradiol level in the postmenopausal range according to institutional standards (or >34.4 IU/L for FSH and <10 pg/mL for estradiol if institutional range is not available) prior to randomization.

  NOTE: *As per local regulations, to demonstrate postmenopausal status, serial measurements of FSH may be required in patients who are not using hormonal contraception or hormonal replacement therapy, and in the absence of amenorrhea for at least 12 months.*
- Pre/perimenopausal women, ie, not meeting the criteria for being postmenopausal.
  - Pre/perimenopausal women can be enrolled if amenable to be treated with goserelin or other GnRH analog approved for use in early breast cancer in the respective countries.

Informed Consent

I 12. Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusions

I 13. Participants with HIV are eligible if the disease is well-controlled with a viral load <200 copies of HIV per mL of blood.

NOTE: *antiretroviral medicines may interfere with IMP, refer to Section 6.8.*

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Multicentric, multifocal and/or bilateral breast cancer of which any histopathological examined lesion is both ER and PgR negative.

E 02. Medical history or ongoing gastrointestinal disorders potentially affecting the absorption of amcenestrant and/or tamoxifen. Participants unable to swallow normally or unable to take tablets and capsules. Predictable poor compliance to oral treatment. Active inflammatory bowel disease or chronic diarrhea, known active hepatitis A/B/C*, hepatic cirrhosis, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection or banding procedures.

NOTE: * *Active hepatitis, defined as: A (positive HA antigen or positive IgM); B (either positive HBs antigen or positive hepatitis B viral DNA test above the lower limit of detection of the assay); C (positive hepatitis C antibody result and quantitative hepatitis C (HCV) ribonucleic acid (RNA) results greater than the lower limits of detection of the assay).*

E 03. Participants with a prior breast cancer history treated with AI

E 04. Any other solid tumor or lymphoma diagnosis is not allowed except if the participant has been free from disease for ≥5 years. Adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer are allowed.

E 05. Pregnant or nursing women, or women of child-bearing potential without a negative pregnancy test prior to randomization.

E 06. Participants with unrecovered acute toxic effects of prior AI therapy or surgical procedures of National Cancer Institute- Common Terminology Criteria of Adverse Events (NCI-CTCAE) Version 5.0 Grade >1 (except alopecia or other toxicities not considered a safety risk for the participant at investigator's discretion).

E 07. Uncontrolled intercurrent illness, including psychiatric conditions that would limit compliance with study requirements.

E 08. Participants with abnormal coagulation profiles, or any history of coagulopathy within 6 months prior to the first dose of IMP including history of deep venous thrombosis (DVT) or pulmonary embolism. However, participants with the following conditions will be allowed to participate:

- Participants with adequately treated catheter-related venous thrombosis occurring more than 1 month prior to the first dose of IMP.
- Participants being treated with an anticoagulant, eg, warfarin, heparin, or direct oral anticoagulants (DOAC; eg, dabigatran, rivaroxaban) for a thrombotic event occurring

more than 6 months before randomization, or for an otherwise stable and allowed medical condition (eg, well-controlled atrial fibrillation) provided dose and coagulation parameters (as defined by local standard of care) are stable for at least 1 month prior to the first dose of IMP.

Prior/concomitant therapy

E 09. Treatment with any SERD, tamoxifen or toremifene are not allowed as prior adjuvant therapy but could have been used as neoadjuvant therapy up to a maximum duration of 3 months. Participants who were treated with a SERD, tamoxifen or toremifene in the neoadjuvant setting and who experienced disease progression are not allowed. Prior treatment with raloxifene or tamoxifen for bone health, risk reduction, or a prior breast cancer is allowed provided this was discontinued at least 3 years before diagnosis of current breast cancer.

E 10. Ongoing treatment with HER2-directed therapy. Appropriate wash out between the last dose of HER2-directed therapy and randomization should be at least 4 weeks.

E 11. Major surgery within 4 weeks before randomization.

E 12. Treatment with drugs that are sensitive substrates of OATP1B1/1B3 (asunaprevir, atorvastatin, bosentan, danoprevir, fexofenadine, glyburide, nateglinide, pitavastatin, pravastatin, repaglinide, rosuvastatin and simvastatin acid) within 2 weeks before first IMP administration.

NOTE: *Refer to FDA website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-1*

E 13. Treatment with strong CYP3A inducers within 3 weeks before first IMP administration.

NOTE: *List of strong CYP3A drugs can be found in section 6.8 concomitant therapy*

E 14. Treatment with drugs that have potential to inhibit UGT, including but not limited, to atazanavir and probenecid, within 2 weeks before IMP administration.

E 15. Treatment with strong inhibitors of CYP2D6 within 2 weeks before first IMP administration **NOTE:** *List of potential drugs interacting with CYP450 can be found at: http://medicine.iupui.edu/clinpharm/ddis/table.aspx*

Prior/concurrent clinical study experience

E 16. Participation within 4 weeks before randomization in any other clinical study involving an investigational study treatment including anti-cancer agents.

Diagnostic assessments

E 17. Inadequate hematological function including:

- Hemoglobin <9 g/dL or blood transfusion support within 2 weeks prior to randomization
- Neutrophils <1.5 x 10^9/L or growth factor support within 2 weeks prior to randomization
- Platelet count <100 x 10^9/L or platelet transfusion support within 2 weeks prior to randomization

E 18. Inadequate renal function with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 as estimated using the Modification of Diet in Renal Disease (MDRD) formula.

E 19. Prothrombin time/international normalized ratio (INR) >1.5 times the upper limit of normal (ULN) or outside therapeutic range if receiving anticoagulation that would affect the prothrombin time/INR.

E 20. Inadequate liver function as defined as:

- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >1.5 x ULN
- Alkaline phosphatase (ALP) >1.5 x ULN
- Total bilirubin >1.5 x ULN (>3.0 x ULN with direct bilirubin within normal range in patients with Gilbert's disease)

Other exclusions

E 21. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 22. Any country-related specific regulation that would prevent the participant from entering the study – see Section 10.8 (Appendix 8) of the protocol (country-specific requirements).

E 23. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 24. Any specific situation during study implementation/course that may rise ethics considerations.

E 25. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

All eligibility criteria must be adhered to. Protocol waivers or exemptions are not allowed.

5.3 LIFESTYLE CONSIDERATIONS

Compliance with the study protocol: Absence of any condition hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial.

5.3.1 Sun protection

A phototoxicity risk for amcenestrant was identified based on the absorption spectrum of the compound in *in vitro* and *in vivo* preclinical studies. Within the amcenestrant development program which includes the below recommendations, cumulatively Grade 1 sunburns were observed only in 2 patients out of an approximately 700 participants exposed so far to amcenestrant doses (from 20 to 1200 mg).

Participants should avoid direct exposure to natural or artificial sunlight during study treatment and for at least 5 days after last amcenestrant/amcenestrant-matching placebo dose. It is recommended to advise to wear protective clothing, lip balm, and broad-spectrum sunscreen with a high sun protection factor (eg, ≥30) to cover UVA and UVB light exposure when outdoors with frequent re-application as necessary.

5.3.2 Osteoporosis

Lifestyle changes that preserve bone mineral density [eg, stopping or reducing smoking and drinking, and increasing physical activity, especially weight-bearing exercises), and adequate nutrition (protein, calcium, and supplementary vitamin D3)] are recommended.

5.3.3 Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE). Only SAEs related to study procedures will be collected from signing of the informed consent form through the time the screen failure is declared.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Participants who are rescreened are required to sign a new informed consent form, and should be assigned a new study participant number, and all the screening procedures should be repeated and entered in the screening visit pages. In case the participant is a temporary

screen failure, there is no need to have participant reconsent (ie, new ICF signed) if the participant finally participates in the trial. However, if the reason for temporary screen failure is a reason that might have altered the initial given agreement of the participant to participate, the Investigator should ensure the willingness of the participant to continue or redo some screening procedures and his/her participation to the trial. This oral agreement should be documented in the participant's chart. All the tests out of protocol window should be repeated and entered to the additional pages.

5.5 CRITERIA FOR TEMPORARILY DELAYING

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Section 10.9 (Appendix 9) should be considered.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention, marketed product and placebo intended to be administered to a study participant according to the study protocol.

The study interventions, Amcenestrant/Amcenestrant-matching placebo and Tamoxifen/Tamoxifen-matching placebo, will be administered as a flat-fixed dose, and not by body weight or body surface area.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 3 - Study intervention(s) administered

Intervention label	Amcenestrant 200 mg (SAR439859)	Amcenestrant matching placebo	Tamoxifen 20 mg	Tamoxifen matching placebo
Intervention name	Amcenestrant 200 mg (SAR439859)	Amcenestrant matching placebo	Tamoxifen 20 mg	Tamoxifen matching placebo
Intervention description	QD-tablet	QD-tablet	QD-tablet	QD-tablet
Type	Drug	Drug	Drug	Drug
Dose formulation	Tablet	Tablet	Tablet	Tablet
Unit dose strength(s)				
Dosage level(s)	1 tablet once a day with food, at approximately the same time every day (±3 hours)	1 tablet once a day with food, at approximately the same time every day (±3 hours)	1 tablet once a day with food, at approximately the same time every day (±3 hours)	1 tablet once a day with food, at approximately the same time every day (±3 hours)
Route of administration	Oral	Oral	Oral	Oral
Use	Experimental active	Experimental placebo	Comparator	Comparator placebo
IMP and NIMP	IMP	IMP	IMP	IMP
Packaging and labeling	Amcenestrant 200 mg will be provided in child resistant bottles (32 tablets per bottle). Labelling will be as required per country requirement	Amcenestrant matching placebo will be provided in child resistant bottles (32 tablets per bottle). Labelling will be as required per country requirement	Tamoxifen 20 mg will be provided in child resistant wallets (32 tablets per wallet). Labelling will be as required per country requirement	Tamoxifen matching placebo will be provided in child resistant wallets (32 tablets per wallet). Labelling will be as required per country requirement
[Current/former name(s) or alias(es)]	Amcenestrant 200 mg (SAR439859)	Amcenestrant matching placebo	Tamoxifen 20 mg	Tamoxifen matching placebo

Table 4 - Study arm(s)

Arm title	A	B
Arm type	Experimental	Active comparator
Arm description	Amcenestrant (SAR439859) 200 mg + Tamoxifen Placebo	Amcenestrant Placebo + Tamoxifen 20 mg
Associated intervention labels	None	None

6.1.1 Treatment starts after randomization

All participants entered into the study will be treated within 3 working days of randomization. A participant may receive additional study interventions if he/she meets retreatment criteria as determined by the Investigator and agrees to be retreated. Throughout the study, study intervention will be blinded.

6.1.2 Patient diaries

Participants will receive study drug diaries for Amcenestrant/Amcenestrant-matching placebo and Tamoxifen/Tamoxifen-matching placebo to document study intervention intake, and the completed study drug diaries should be returned to the study site at the subsequent study visit.

6.1.3 Drug dispensation

IMPs are dispensed at each protocol-scheduled on-site visit as defined in the SoA (Section 1.3 "IMP dispensation call" raw). Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, IMPs may be supplied from the PI/site to the participant via a Sponsor-approved courier company where it was allowed by local regulations and agreed up on by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 10.9 (Appendix 9): Contingency measures for a regional or national emergency that is declared by a governmental agency.

6.1.4 Amcenestrant/Amcenestrant-matching placebo

Amcenestrant/Amcenestrant-matching placebo will be administered orally at a dose of 200 mg once daily in fed condition and at approximately the same time each day (±3 hours), together with Tamoxifen/Tamoxifen-matching placebo. The daily dose of amcenestrant (SAR439859) tablets is to be swallowed whole with water. The two tablets should be taken within 5 minutes. Study participants should be instructed not to bite or chew on the tablets.

6.1.5 Tamoxifen/Tamoxifen-matching placebo

Tamoxifen/Tamoxifen-matching placebo will be administered orally at a dose of 20 mg once daily and at approximately the same time each day (±3 hours), together with Amcenestrant/Amcenestrant-matching placebo. The two tablets should be taken within 5 minutes. Study participants should be instructed not to bite or chew on the tablets.

Refer to the Tamoxifen Summary of Product Characteristics for additional administration instructions.

6.1.6 Non-investigational medicinal products

Goserelin or other GnRH analog, approved for use in early breast cancer as per site/country availability, will be administered in male participants without prior orchiectomy and in pre/perimenopausal women.

Refer to the corresponding Summary of Product Characteristics for additional administration instructions.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. The investigator, institution, or the head of the medical institution is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Partially used and used study intervention will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist). A detailed treatment log form of the destroyed study intervention will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator must not destroy the unused IMP unless Sanofi provides written authorization. Further guidance and information for the final disposition of used and unused study medications are provided in the pharmacy manual and/or monitoring plan.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.7).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Two systems requiring log in by the investigator will be used:

- Medidata Rave EDC system, to be used to complete the eCRF
- The IRT system for registration, randomization and drug supply information

Both systems are accessible 24 hours a day, 7 days a week.

The log in instructions for Rave EDC system and IRT system will be provided to each investigator prior to site authorization.

Screening and randomization will be performed in three steps:

- **Step 1: Screening**

  Participants will be recorded directly in the IRT system. At this stage, date of signature of informed consent and questions related to stratification factors (see Section 4.1) should be completed. Patient identifier will be created. In parallel, tumor sample has to be sent for central pathology assessment to confirm ER and PgR status.

- **Step 2: Eligibility criteria data collection and central confirmation of ER and PgR biomarkers**

  Once a patient is registered in the IRT system, the investigator should log in on the Medidata Rave EDC system, to complete the eligibility related baseline information.

  Note that the tumor material shipment and imaging work up can be performed while patient is still treated with AI. The other assessments/questionnaires required before randomization should be performed/completed when the participant is off the prior AI therapy.

- **Step 3: Randomization**

  Once eligibility criteria, ER / PgR status and discontinuation of prior AI therapy due to treatment-related toxicity have been confirmed, the participant could be randomized in the IRT system. During this step, stratification factors should be confirmed in the IRT system.

  - The randomized intervention kit number list is generated centrally by Sanofi.
  - The IMPs are packaged in accordance with this list.

- The randomization and intervention allocation are performed centrally by an IRT. The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it. Details of the IRT procedure will be provided in the IRT Site Manual.
- Participant cannot be randomized more than once in the study.
- Warning: the randomization will not be possible if study treatment and ER/PgR central results are not available at site. Please consider adequate timeframe.

Methods of blinding

- As per the double blind and double-dummy design, all randomized patients will also receive the matching-placebo corresponding to the other treatment arm. Amcenestrant-matching placebo will be supplied as tablets identical to amcenestrant 200 mg tablets in appearance. Tamoxifen-matching placebo will be supplied as tablets identical to tamoxifen 20 mg tablets in appearance. IMPs (amcenestrant, tamoxifen) and their matching-placebo will be supplied in indistinguishable boxes
- The EORTC and the SANOFI study teams will be blinded to treatment allocation until the database lock for the primary analysis of the primary endpoint IBCFS. An independent unblinded statistician will be appointed by the EORTC HQ in order to prepare confidential reports for the IDMC reviews. Other intermediate reports (safety reports, data surveillance report, newsletters) issued before the primary analysis of IBCFS endpoint will be prepared by the blinded study teams. Medical review will be conducted blinded to treatment allocation.

Unblinding

The investigator and the site staff may be unblinded in one of the following cases:

- Emergency unblinding: In case of emergency, the investigator has the sole responsibility to decide if unblinding of the participant's treatment allocation is warranted. The Investigator should make every effort to contact the Sponsor and/or Sponsor's representatives prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. The unblinding requests should be made by the investigator through the IRT system. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable. If the code is broken, the participant must withdraw from the IMP administration.
- Unblinding after the first IBCFS event: Blinding codes may also be broken after a patient discontinues treatment due to disease recurrence, as determined by the treating investigator, but only if deemed essential to allow the investigator to select the patient's next treatment regimen and after discussion and agreement with the Sponsor.
- Code should not be broken in the absence of emergency situations or disease recurrence.
- The blinded EORTC statistician and the Sponsor's statistician will receive the treatment allocations after the database lock for the primary analysis of the primary endpoint IBCFS.
- Sponsor's safety team may unblind the treatment allocation assignment for any participant with an SAE.

6.4 STUDY INTERVENTION COMPLIANCE

Administration of the IMP will be supervised by the Investigator or Sub-investigator.

IMP accountability:

Intervention units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).

The Investigator counts the number of tablets, remaining in the returned packs, and fills in the Intervention Log Form.

The Investigator records the dosing information on the appropriate page(s) of the CRF.

The monitor in charge of the study then checks the CRF data by comparing them with the IMP which he/she has retrieved and intervention log forms.

At each dispensation visit, when participants are dispensed with study intervention at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. On days when there are no on-site visits, study participants will take the study intervention at home. The study staff will demonstrate to the patient how to record information on study intervention intake in study medication diary. Study participants will have to complete the study medication diary and the completed study medication diary should be returned to study site at subsequent site visit. In case of an early vomiting event, the administered dose of study intervention should not be repeated.

When participants take study intervention at home, compliance with study intervention will be assessed at each visit, using study medication diaries and study medical record (study source documentation). Compliance will be assessed by direct questioning, counting returned tablets during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of amcenestrant/amcenestrant-matching placebo, tamoxifen/tamoxifen-matching placebo tablets and goserelin or other GnRH analog, dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for IMP omissions and NIMP delays/omissions will also be recorded in the CRF.

6.5 DOSE MODIFICATION

No dose reduction of study intervention is permitted. Dose adjustment in case of treatment-related toxicity is managed by dose omission.

Dose adjustment guidelines for study intervention (amcenestrant/amcenestrant-matching placebo and tamoxifen/tamoxifen-placebo) in case of treatment-related toxicity could be found in Section 10.10.1 (Appendix 10).

6.5.1 Missed doses

- Any doses of study intervention that are not taken within 6 hours of the intended time should be considered as missed dose.
- If the participant misses a dose of study intervention, a double dose should not be taken the next day to compensate the missed dose.
- If the participant vomits a dose of study intervention, an additional dose should not be taken, and this information must be recorded in the study medication diary. The next prescribed dose should be taken at the usual time.
- Doses omitted for toxicity are not to be replaced within the same cycle.

6.5.2 Retreatment criteria in case of treatment-related toxicity

Study treatment may be held up to 28 days to permit sufficient time for recovery from the toxicity. For patients not recovering from toxicity within 28 days, a delay >28 days is permitted if the patient benefits from the study intervention; the investigator will contact the Sponsor or Sponsor's representatives for the retreatment. In absence of clinical benefit, permanent discontinuation of the study intervention should be considered.

6.5.3 Restarting study medications following treatment interruption

The criteria for restarting study medication following an interruption that was unrelated to toxicity from study intervention, examples including:

- For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9 (Appendix 9): Contingency measures for a regional or national emergency that is declared by a governmental agency.
- Patients with diagnosis of second non-breast primary invasive cancers may be considered for temporary discontinuation (treatment temporarily suspended to allow for local treatment of the second non-breast primary cancer).
    - If the interruption does not exceed 3 months in any 12-month time period with systemic therapy not required and no evidence of breast cancer recurrence, study treatment can be re-started.
    - If the interruption >3 months and the patient benefits from the study intervention, the investigator will contact the Sponsor or Sponsor's representatives for the retreatment. In absence of clinical benefit, permanent discontinuation of the study intervention should be considered.
- If Sponsor or Sponsor-representative's approval to restart/rechallenge participant with study intervention is not granted, then participant must permanently discontinue study intervention and may continue in the study for protocol-specified follow up assessments.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

After normal completion of the IMP, patient will not receive additional doses.

6.7 TREATMENT OF OVERDOSE

In the event of an overdose, the Investigator should:

1. Contact the Sponsor or Sponsor representatives immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until recovery to Grade ≤1
3. Document appropriately in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor or Sponsor representatives based on the clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

The Sponsor or Sponsor representatives should be contacted if there are any questions regarding concomitant or prior therapy. The following therapies/medications are prohibited throughout the active treatment phase in relation to amcenestrant and/or tamoxifen treatment:

- Any concurrent anti-cancer treatment (surgery, radiotherapy, systemic therapy) except for participants diagnosed during the study with a second primary malignancy not requiring systemic therapy (ie, chemotherapy, hormonal therapy, targeted therapy, etc) and for whom study treatment is temporarily suspended to allow local treatment (surgery and/or radiation).
- Drugs that are strong inducers of CYP3A (including St John's Wort and genistein used as herbal medicine or food supplement, rifampin, avasimibe, rifapentine, phenytoin, carbamazepine, lumacaftor, phenobarbital) since they may decrease amcenestrant exposure.
- Drugs that are sensitive substrates of OATP1B1/1B3 including asunaprevir, atorvastatin, bosentan, danoprevir, fexofenadine, glyburide, nateglinide, pitavastatin, pravastatin, repaglinide, rosuvastatin and simvastatin acid, since amcenestrant is a potential inhibitor and may decrease their elimination.

- Drugs that are UGT inhibitors, including but not limited to atazanavir and probenecid, since amcenestrant is substrate of UGT1A1 and UGT1A4 and they may increase amcenestrant exposure.
- Drugs that have an influence on the status of sex hormones, ie, additional hormonal treatments (either oral or transdermal) including estrogen, progesterone hormone replacement therapy, oral or other types of hormonal contraceptives (including implants and depot injections).
- Strong and moderate inhibitors of CYP2D6 (eg, paroxetine, fluoxetine, quinidine, cinacalcet, bupropion, duloxetine, sertraline, trazodone, thioridazine, perphenazine, pimozide, clomipramine, terbinafine, diphenhydramine, amiodarone, cimetidine, chlorpromazine) since they could lead to reduced efficacy of tamoxifen.

Special caution should be taken with regards to the following therapies in relation to amcenestrant treatment:

- Drugs that are sensitive substrates of CYP3A, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGTs since it may result in loss of efficacy of these agents. Monitor patients for loss of efficacy if use of these medications, or substitute.
- Note refer to the **list of potential drugs interacting with CYP450 can be found at: http://medicine.iupui.edu/clinpharm/ddis/table.aspx**
- Warfarin: a marked increase in anticoagulant effect may occur when tamoxifen is used in combination with warfarin. Closely monitor coagulation indices in patients who require concomitant use of warfarin.

The following concomitant treatments are permitted during this study:

- Bisphosphonates may be used in post-menopausal patients (including pre/peri menopausal participants treated with GnRH analogs) as per local protocols.
- Vaccines for COVID-19 infection:

  If investigators decide to administer SARS-CoV-2 vaccines in patients enrolled in the study, decisions should be individualized based on the risk of SARS-CoV-2 complications and potential benefit from the vaccine, general condition of the patient and the severity of COVID-19 outbreak in a given area or region and in accordance with the vaccine label. Furthermore, the Country guidelines and/or institutional guidelines, must be followed.

  The available SARS-CoV-2 vaccines, that are not live attenuated vaccines, are not contra-indicated in patients on anticancer treatment.

  Treatment schedule should not be altered because of the COVID-19 vaccination.

  The administration of a SARS-CoV-2 vaccine (including brand name) shall be added in the concomitant medication form in the eCRFs and noted in the patient's Medical file. Any vaccine related AE(s) should be captured in the AE forms in the eCRFs.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

Study Intervention will be continued until the occurrence of one of the following criteria:

- Normal completion of the study intervention (5 years)
- Recurrence as defined in Section 9.2.2.
  - After the recurrence, the study intervention may be unblinded upon request of the investigator
- In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for the study endpoints unless she/he withdraws consent.
  - The investigator has the right to remove any participant (eg, poor compliance to the protocol, intercurrent illness that prevents further administration of study intervention) from study.
- Participant's request
- Administration of the study intervention will be discontinued in the event of a TEAE that persists despite appropriate measures or any other AE that, in the opinion of the Investigator, warrants discontinuation (Section 6.5.2, Section 8.3.5).
- Study intervention interruption exceeding 3 months, in absence of clinical benefit and approval from the Sponsor or Sponsor's representatives as per Section 6.5.3
- In case of unblinding, the participant must discontinue study intervention as per Section 6.4.

7.1.2 Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.3 Extended adjuvant endocrine therapy

Extended adjuvant endocrine therapy upon completion of study treatment is allowed. Treatment recommendation should be considered on an individual patient basis taking into consideration clinico-pathologic characteristics, patients' preferences, and total duration of adjuvant endocrine therapy at the time of study treatment completion or discontinuation. When extended adjuvant endocrine therapy is considered, treatment options include adjuvant tamoxifen or adjuvant aromatase inhibitor.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant who withdraws from the study will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study for the follow up visits.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be directly or indirectly contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.10 (Appendix 1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Participants still on AI treatment may enter the screening period for central confirmation of biomarkers and screening imaging assessments. The other assessments and questionnaires required before randomization will be performed and completed when patient is off the AI therapy.
- For each participant, the follow-up period is defined from EOT to up to 10 years from randomization except in case of premature study termination due to one of the following reasons: withdrawal of consent, loss to follow-up or death.

8.1 EFFICACY ASSESSMENTS

8.1.1 At Screening

- **Mammogram**

At screening (within 28 days prior to randomization), mammogram* is required if not already done in the past 6 months prior to randomization.

* If local investigator plans to use breast MRIs instead of mammograms during the study, breast MRI will have to be performed at screening

Note: women with prior bilateral mastectomy should not get mammograms (or breast MRIs).

- **Baseline staging**

Baseline staging to document the absence of metastatic disease must be performed within 28 days prior to randomization for patients at highest clinical risk for disease recurrence:

- Participants with symptoms suggestive of metastatic disease indicated per investigator's judgment

- Participants diagnosed with stage IIIA or higher and no staging evaluation prior to study enrollment.

Staging must include chest, abdominal ± pelvic and bone imaging and clinical evaluation of superficial disease. Examination type for imaging staging can include sonography, bone scan, CT, MRI and/or PET-CT as per investigator's choice.

8.1.2 Post baseline

- **Mammogram/breast MRI**

Mammogram (or breast MRI) will be performed on yearly basis from randomization (± 30 days), and as clinically indicated until the detection of locoregional recurrence and distant recurrences (whichever comes last) or end of follow-up period, whichever comes first.

- **CT Scan/MRI/Other imaging**

The post baseline imaging work-up will be done as clinically indicated until the detection of locoregional recurrence and distant recurrences (whichever comes last) or end of follow-up period.

The imaging work-up can include: Radionuclide Bone Scan Whole Body, CT Scan, MRI, PET-CT, Ultrasound of Chest, Abdomen, Pelvis or any clinically indicated sites of disease and clinical evaluation of superficial disease.

- **Biopsy**

Disease recurrence should be confirmed histologically whenever possible.

Note: for the locoregional recurrence including skin recurrence it is recommended to perform a biopsy unless clinically contra-indicated.

8.1.3 Overall survival follow-up

After discontinuation of study treatment, follow-up visits will be performed every 12 months (±45 days) from the last dose of study treatment for survival status and collection of data on post-study anticancer therapies, and disease recurrence for patients who complete or prematurely discontinue study treatment without disease recurrence.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A physical examination should include, at a minimum, assessments of the cardiovascular system, pulmonary system, gastrointestinal system (including palpation of liver and spleen), examination of the skin, and breast exam (palpation of breast/chest wall, axillae, supra- and infraclavicular regions). Height (at baseline only) and weight will also be measured and recorded. Investigators should pay special attention to clinical signs related to previous serious illnesses.
- A gynecological examination should be performed at least on a yearly basis according to the schedule provided in the SoA (see Section 1.3), or more frequently in case of sign or symptoms of endometrial abnormality (eg, abnormal bleeding). The examination should be performed as per the site's local guidelines and the result should be reported as either normal or abnormal.
- Any new finding or worsening of previous finding should be reported as a new adverse event.

8.2.2 Vital signs

- Body temperature, blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Systolic and diastolic blood pressure, and pulse rate will be measured in a semi-supine position after 5 minutes rest.
- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- Vital signs and ECG abnormalities are to be recorded as adverse events only if they are symptomatic and/or requiring corrective treatment and/or leading to treatment discontinuation and/or dose modification and/or fulfilling a seriousness criterion (see Section 10.3 [Appendix 3]).

8.2.3 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. Laboratory abnormalities are to be recorded as adverse events only if they lead to treatment discontinuation and/or dose modification and/or fulfill a seriousness criterion and/or are defined as an AESI (see Section 10.3, [Appendix 3]).

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor or Sponsor's representatives notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 8.2).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3 and until at least 30 days after administration of the last study intervention. After this period, all ongoing related AEs, all ongoing SAEs regardless of relationship with study treatment, and all new related AEs (serious or nonserious), are to be reported and followed up until resolution or stabilization. All SAEs and AESI will be recorded and reported to the Sponsor or Sponsor's representatives immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and AEs of special interest (as defined in Section 8.3.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information (IB for Amcenestrant and SmPC or package insert for other IMP)
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB or state other documents and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until:

- The 30 days after the last study treatment administration for female participants.

- The 30 days after the last study treatment administration for female partners of male participants.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Pregnancy of female participant will lead to definitive discontinuation of study intervention.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse event of special interest

Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP.
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.
    Of note, asymptomatic overdose should be reported as a standard AE.
- Increase in alanine transaminase (ALT) ≥ Grade 3.
  - Omit study-treatment study-intervention administration and repeat LFTs within 2-3 days. If not recovered, monitor LFTs weekly until recovery to Grade ≤1 (or baseline grade). Confounding factors such as, liver metastasis, hepato-biliary disorders, concomitant medications, etc. should be excluded prior to dose modifications. Please refer to the dose modification guidelines for management of increase of ALT. [Appendix 10 (Section 10.10.1)].

- Close monitoring of study participants is recommended in cases of increase of Grade ≥3 ALT. LFTs should be performed in patients with onset of otherwise unexplained nausea, jaundice, right upper abdominal pain, fever, or rash.
- LFTs include AST, ALT, ALP (isoenzymes if Grade >2), direct bilirubin, indirect bilirubin, GGT, and INR (if total bilirubin >2.5 ULN).
- An ultrasound, or other imaging of liver, should be considered based on the clinical presentation.
- A consultation with a hepatologist should be undertaken if there is,
  - Unexplained or persistent Grade ≥3 ALT despite dose omissions.
  - ALT >3 ULN and concomitant jaundice (total bilirubin >2.5 ULN), in patients with normal ALT and total bilirubin at baseline.
  - to exclude hepato-biliary disorders (eg, hepatotropic virus infections, autoimmune or alcoholic hepatitis, Non-Alcoholic Steatohepatitis, etc) or drug induced liver injury.
- Further hepatic virology will be undertaken as per the site's local guidelines for the treatment of cancer patients, considering the local and national recommendations.

- Photosensitivity
  - If photosensitivity is suspected in study participants, consider dermatologist consultation. Confounding factors such as other dermatological disorders, drug eruptions resulting from concomitant medication use, etc. should be excluded prior to any dose modification (refer to Section 10.10.1 [Appendix 10] for treatment-related dose modification for non-hematological toxicities). In case of study intervention discontinuation because of photosensitivity reaction, study participant should be followed for possibility of development of other manifestations of photosensitivity such as photo-onycholysis, lichenoid reaction or actinic granuloma.

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 PHARMACOKINETICS

Whole blood samples will be collected from all participants for measurement of blood concentrations of amcenestrant using Dried Blood Spot (DBS) at time points specified in the SoA (Section 1.3) and additional information is provided in the sample Table 5 (Section 8.6.2). An aliquot of plasma will be prepared on C2 and C7 in a subset of patients to determine the Blood/Plasma ratio. Approximately 300 plasma samples (of which, approximately 100 samples

from Chinese patients) will be collected for the determination of Blood/Plasma ratio for amcenestrant. Plasma aliquot prepared and available in the Lab after the cutoff date for amcenestrant assay in plasma may not be assayed and may be discarded.

The timing of sampling may be altered during the course of the study based on newly available data to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor or Sponsor's representatives in a separate document (Central Laboratory Services Manual). The actual date and time (24-hour clock time) of each sample will be recorded. Pharmacokinetic samples will be tested by the Sponsor or Sponsor's representatives.

Samples collected for analyses of amcenestrant concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Pharmacokinetic samples could also be used for testing analytical method performance such as comparability and incurred sample reproducibility, and for possible exploratory analysis of drug metabolites. The exploratory data may not be included in the study report but will be kept on file.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. The bioanalysts responsible for the sample analysis will be unblinded. They will, however, agree not to disclose the randomization schedule or the individual unblinded analytical results before the official opening of the randomization schedule.

A population PK approach may be used to determine amcenestrant PK parameters. The determined Blood/Plasma ratio could be used to convert blood concentrations to plasmatic concentrations to compare AMEERA-6 PK parameters to plasmatic exposures obtained in others amcenestrant studies.

8.5 GENETICS

The genomic DNA (gDNA) for the translational research studies will be extracted from a blood sample collected from participants (see sample Table 5 (Section 8.6.2) for the sample specifications). The gDNA material will be only used for the elimination of the non-somatic variants of the tumor genetic studies and it will not be subject of any study by itself.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent (see sample Table 5 below for the sample specifications).

The tumor genomic material will be extracted from the FFPE tumor tissue collected at baseline and EOT for patients that discontinued the treatment due to disease progression, and will be collected for DNA and RNA isolation from all participants [see sample Table 5 (Section 8.6.2) for the sample specifications]. Participation is mandatory for the baseline analysis. [See Appendix 5, Section 10.5) for information regarding genetic research]. Details on processes for collection, shipment and destruction of these samples can be found in the laboratory manual.

The genetic findings will be reported to the sites.

8.6 BIOMARKERS

8.6.1 Rationale

8.6.1.1 Biomarker evaluations

The overarching goal of the AMEERA-6 correlative science objectives is to investigate whether tumor-derived biomarkers assessed using tumor tissue and blood specimens predict benefit from amcenestrant compared to tamoxifen.

The comprehensive collection of biospecimens will enable next generation sequencing technologies, protein, or metabolite-based assays aiming to identify predictors of treatment benefit and/or markers of resistance.

The tumor tissue specimens will be profiled using DNA and RNA sequencing to generate a comprehensive "in silico" platform allowing the investigation of correlative science questions in an unbiased manner. Residual tumor specimens stored in the study biorepositories will enable validation of correlative science findings and additional research following the endorsement from the study Steering committee.

The molecular classification of breast cancer (60, 61) has allowed us to understand the natural history of different subtypes of this disease including Luminal A, Luminal B basal-like and HER2-enriched. The RNA sequencing data will allow us to evaluate the benefit of amcenestrant compared to tamoxifen across its major molecular subtypes.

8.6.1.2 Endocrine sensitivity

Of importance, AMEERA-6 includes a comprehensive plan dedicated to evaluate the relative effectiveness of amcenestrant versus tamoxifen according to measurements of endocrine sensitivity through $SET_{2,3}$ and/or other measurements of endocrine sensitivity.

$SET_{2,3}$ is a CLIA-compliant test that is applied to FFPE tissue sections and accurately measures endocrine-related transcriptional activity ($SET_{ER/PR}$ index) that is then adjusted for baseline prognosis (T, N, RNA4) (62). The test measures 31 transcripts and has already demonstrated pre-analytical and analytical validity, including inter-laboratory reproducibility.

The $SET_{ER/PR}$ index measures endocrine hormone receptor related transcriptional activity. The signature was designed to represent genes with strong correlation to both ER and progesterone receptor transcription, with exclusion of genes known to have a principal role in proliferation. Therefore, the design of the $SET_{ER/PR}$ signature was intended to represent endocrine related transcription exclusive of the obviously prognostic effect of proliferation. Since estrogen activation of estrogen receptor has a profound effect on overall transcriptional profile, we can reasonably infer that the $SET_{ER/PR}$ provides a measure of endocrine dependent activity in the cancer cells. The exclusion of the few obviously proliferative genes from the $SET_{ER/PR}$ signature

(eg, cyclin D1) was specifically to avoid confounding influences of baseline molecular prognosis. The extent of endocrine related activity in a breast cancer has a relationship to prognosis, but its endocrine predictive information is expected to be stronger due to the biological rationale that greater endocrine-dependent cellular activity predicts greater susceptibility to targeted inhibition by endocrine therapy.

The $SET_{2,3}$ index was developed to represent the endocrine related transcription activity in the cancer sample ($SET_{ER/PR}$) adjusted for its baseline prognostic index. Thus, $SET_{2,3}$ assay measures the weighted sum of $SET_{ER/PR}$ and a baseline prognostic index that is derived from tumor stage, nodal metastases, and molecular subtype. Essentially, $SET_{2,3}$ assay measures endocrine activity in the context of the natural baseline prognostic biology. In its simplest form, molecular subtype has been meaningfully represented using immunohistochemistry for just four proteins per (IHC4), namely estrogen receptor, progesterone receptor, HER2 receptor, and the proliferation marker Ki67. A baseline prognostic index used on $SET_{2,3}$ recapitulates this by using RNA4 that is derived from the following four transcripts: estrogen receptor, progesterone receptor, HER2 receptor, and delete the proliferation gene after aurora kinase A.

8.6.1.3 Material and methods

Collection of samples for the defined and other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3, and see sample Table 5 [Section 8.6.2] for the sample specifications):

- Blood
- Tumor FFPE tissue block at baseline (the most recent archived tumor FFPE sample)

Optional samples for biomarker research that should be collected from participants in the study where possible are the following:

- Tumor FFPE tissue at end of treatment (for patients who discontinue treatment due to disease recurrence)

8.6.1.4 Objectives

- Tumor protein biomarkers, such as ER, PgR, Ki67, and Bcl-2 protein expression by immunohistochemistry, endocrine sensitivity transcriptome evaluation (eg, SET index), ER activation score, artificial intelligence-based image analysis, gene expression/genomic aberration profile (in RNA and DNA including WES) and in archival and optional FFPE biopsy for participants who discontinued treatment due to disease recurrence to evaluate their association with the observed clinical responses to endocrine sensitivity.
- To study the histological type studies (ductal, lobular, others) of the samples to investigate the predictive and prognostic value.
- To retrospectively study tumor specimen gene expression profile (in RNA) including, but not limiting to with different scores (such as PAM50) in archival to evaluate recurrence risk and breast cancer molecular subtypes, as well as endocrine sensitivity/resistance by

RNA-based multigene assays. Extensive genomic landscape profiling, including whole transcriptome and mutational profiling by whole exome sequencing will also performed to characterize tumors and their characteristics.

- To retrospectively study the ctDNA in blood at pre-treatment, on treatment, and upon disease recurrence to evaluate recurrence risk by ctDNA status and to evaluate genomic landscape and tumor burden, at baseline and changes over time by ctDNA analysis.

For future/non-defined research:

- Blood samples will be collected for proteomics studies in plasma.

In addition, the samples will be stored, and analysis will be performed:

- On other biomarker variants for the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity.
- For the identification of new drug targets or biomarkers that predict participant response to the treatment including new genes/genome candidates, serum analytes, or tissue biomarkers to evaluate their association with observed clinical responses to amcenestrant (SAR439859) versus tamoxifen.

The samples may be used for non-defined research to possibly further study the disease biology, to develop methods, assays, prognostics studies and/or companion diagnostics related to the biology of the disease, pathways associated with the disease state, and/or the mechanisms of action of the drug.

8.6.2 Sample table

The collection of all samples is mandatory for the sites.

Table 5 - Data collection of biological samples

Patient's choice yes[a]/no[b]?	Specimen type(s)	Size/type of sample	Collection time point(s)	Purpose of use	Estimated/ expected sample size
No	FFPE	1xblock (preferred) or 25 slides	Baseline (most recent archived FFPE biopsied tumor tissue samples)	Central review and Biomarker research	1x3738
Yes	FFPE	1xblock or 25 slides	Biopsy collected at EOT for patients who discontinue treatment due to disease recurrence	Biomarker research and endocrine sensitivity study	1x3738 maximum of samples
No	Blood	1x s-monovette edta 1,2 mL tube (DBS and plasma)	Predose sample on C2, C7, C13 and C25	DBS for the PK study	4x3738 (blood)
				Plasma aliquot on C2 and C7 only, to determine Blood/Plasma ratio	approx. 300 plasma samples

Patient's choice yes[a]/no[b]?	Specimen type(s)	Size/type of sample	Collection time point(s)	Purpose of use	Estimated/ expected sample size
Yes	Blood	1xSTRECK 10 mL tube (proteomics studies)	Pre-dose sample on C1D1, C2D1 and upon disease recurrence	Proteomic studies for future research	3x3738 maximum of samples
No	Blood	1xEDTA 2 mL tube (for gDNA)	Pre-dose (C1D1)	Biomarker and genomic research	1x3738
		2xStreck 10 mL tubes (plasma for ctDNA)	Pre-dose (C1D1), pre-dose C2D1 and upon disease recurrence.		6x3738 maximum of samples

a "yes" means that the collection of this material is optional, as patients are given the choice in the Informed Consent Form (ICF). EORTC will not collect this type of material from patients not having specifically consented to this.

b "no" means that the collection of this material is mandatory for the study and patients are not given the choice in the ICF. If patients do not agree with sample collection, they cannot participate in the study

Abbreviation: gDNA = genomic DNA; DBS= dried blood spot

8.7 IMMUNOGENICITY ASSESSMENTS

Immunogenicity is not evaluated in this study.

8.8 HEALTH ECONOMICS

Not Applicable for this study.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.4) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to endocrine breast cancer treatment, and the disease and its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

Remaining leftover samples will be used only after the study ends, ie end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects. Data and samples will be used in alignment with the information provided to participants in the ICF Part 2 (future research). For future research projects, all biological samples and relating data to be used will be coded such that no participant direct identifiers will be linked to them. These coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.5).

Biological samples for future research will be stored for up to 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed, and related coded data will be anonymized unless otherwise required by applicable laws. Relating data for future research will be stored for 25 years after the end of the study.

Participant's coded datasets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

8.10 PATIENT REPORTED OUTCOMES (PROS)

There are no PRO-specific eligibility criteria. All patients enrolled in the trial are expected to fill out the PRO questionnaires according to the pre-defined schedule in the SoA (Section 1.3), unless the required language translation is not available. If no validated translation exists for part of the questionnaires, then the validated portion of the questionnaire set will be administered to the patient.

As stated in the SoA (Section 1.3), PRO measures are to be administered to each study participant after informed consent and prior to any treatment- or study- related activities, including administration of IMP, laboratory work, radiological assessments, discussion with the participant regarding their treatment or health status, and similar activities. The administration schedule for PRO assessments must be adhered to as much as possible, regardless of protocol deviations. As applicable in the SoA (Section 1.3), the PRO instruments will always be administered in the following standardized order: FACT-GP5, EORTC QLQ-C30, EORTC QLQ-BR23, EORTC QLQ-IL127, PRO-CTCAE™, EQ-5D-5L, PGIS, PGIC and MMAS-8. The PRO assessment schedule was designed to correspond with: clinical expectations regarding the onset and duration of symptomatic AEs; expectations regarding the timeframe in which observed changes in the concepts of interest are likely to occur; trial research objectives; trial duration; the dosage level and route of IMP administration; and other prespecified trial endpoints.

All PRO questionnaires are designed for self-completion.

The primary mode of administration is via electronic clinical outcome assessment (eCOA) using an application on participants' own devices. If the eCOA application fails, a web-based eCOA platform will be used as a back-up option. Provisioned back-up devices will be available at each site for participants without their own devices. Training for site staff and patients will occur according to the standards of the eCOA provider. Where participants completed their PRO assessment (ie, home versus site) will be documented. The clinical report forms will include a question whether the PRO assessments have been filled in, and if not, the reason why. It is recommended that a key person (eg, research nurse) not directly involved in the participant's clinical care at each institution should be responsible for questionnaire data collection in order to optimize the participant compliance and to ensure the completeness of the data.

In case, patients are not be able to physically attend hospital visits due to unforeseen restrictions (eg, COVID-19 pandemic restrictions), the PRO data can be collected by electronic assessment at home. Patients should be instructed to complete the questionnaires within the intended timepoint (according to protocol SoA).

Nine PRO questionnaires will be used in this trial: FACT-GP5, EORTC QLQ-C30, EORTC QLQ-BR23, EORTC QLQ-IL127, PRO-CTCAE™, EQ-5D-5L, PGIS, PGIC and MMAS-8. Together, these questionnaires present up to 97 questions to the patients which can be completed in 30-45 minutes.

8.10.1 FACT-GP5

The FACT-GP5 ("I am bothered by side effects of treatment") is a single-item from the Functional Assessment of Cancer Therapy-General (FACT-G) scale (63). Responses are given on a 5- point Likert-type scale recalling the past 7 days. Higher scores indicate a higher degree of side effect bother (64). The FACT-GP5 has been translated in over 50 languages according to a standardized translation procedure (65).

8.10.2 EORTC QLQ-30

The EORTC Quality of Life Questionnaire (QLQ-C30) version 3 (66) is valid for any cancer population and is composed of thirty distinct questions that are scored into fifteen multi-item and single-item scales (67). These include a global health status/QoL scale (2 items), five functional scales (physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), and social functioning (2 items)); eight symptom scales (fatigue (3 items), nausea and vomiting (2 items), pain (2 items), dyspnoea (1 item), insomnia (1item), appetite loss (1 item), constipation (1 item), diarrhoea (1 item)); and a financial difficulties scale (1 item). The questionnaire employs 28 4-point Likert-type scales with responses from "not at all" to "very much" and two 7-point Likert-type scales for global health and overall QOL. For functional and global QOL scales, higher scores represent a better level of functioning and are converted to a 0 to 100 scale. For symptom-oriented scales, a higher score represents more severe symptoms. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups (68, 69). The average time to complete the questionnaire is approximately 10 minutes. The EORTC QLQ-C30 version 3 has been translated in over 50 languages according to a standardized translation procedure (70).

8.10.3 EORTC QLQ-BR23

The EORTC QLQ breast cancer module (QLQ-BR23) is a 23-item disease-specific patient-reported outcome measure of disease-related symptoms, treatment-related symptoms, and functioning relevant to patients with breast cancer. The QLQ-BR23 has been validated for use in conjunction with the QLQC30 (68, 71). The QLQ-BR23 consists of 23 4-point Likert scales with responses from "not at all" to "very much" which are scored into both multi-item scales and single-item scales, including: four functional scales (body image (4 items), sexual functioning (2 items), sexual enjoyment (1 item), and future perspective (1 item)); and four symptom scales (systemic therapy side effects (7 items), breast symptoms (4 items), arm symptoms (3 items), upset by hair loss (1 item)). The scoring principle is similar to the QLQ-C30 (67) with higher scores on the functional scales indicating higher levels of functioning and higher scores on the symptom scales indicating higher symptom levels. The average time to complete the questionnaire is approximately 10 minutes. The EORTC QLQ-BR23 has been translated in over 50 languages according to a standardized translation procedure (70).

8.10.4 EORTC QLQ-IL127

In addition to the QLQ-C30, the EORTC Item Library (72) was used to construct an ad-hoc item list specific to this study. The aim was to add items from the EORTC CAT physical functioning questionnaire (68) in order to obtain an extended, more precise physical functioning scale. A total of 3 items were selected to include self-assessment on physical functioning:

1. Do you have any trouble carrying a heavy bag upstairs?
2. Do you have any trouble taking a long walk carrying a heavy pack on your back (eg, a filled rucksack)?
3. Do you have any trouble hiking 3 km/2 miles on uneven surfaces?

These questions are taken from the validated QLQ-CAT physical functioning questionnaire. Although this Item List is not a validated instrument, it is an ad-hoc instrument optimized for this specific setting and composed of integral parts of validated HRQL questionnaires. All three questions follow the same structure using a 4-point Likert scales with responses from "not at all" to "very much" and are translated according to a standardized translation procedure (72). These three questions will be scored together with the 5 physical functioning items of the QLQ-C30 according to the CAT scoring procedure into an extended physical functioning scale.

8.10.5 PRO-CTCAE

The National Cancer Institute PRO-CTCAE™ was developed to evaluate symptomatic adverse events (AEs) by self-report among patients participating in cancer clinical trials (73, 74). The PRO-CTCAE item library includes 124 items that represent 78 symptomatic AEs in the clinician reported CTCAE. PRO-CTCAE items chosen for this study were systematically selected from the PRO-CTCAE item library to measure 14 symptomatic AEs (representing 24 items) known to be associated with amcenestrant and/or tamoxifen. PRO-CTCAE items included in this study assess the frequency, severity, interference, and/or presence/absence of the following 14 symptomatic AEs: hot flashes (2 items; frequency and severity); increased sweating (2 items; frequency and

severity); joint pain (3 items; frequency, severity, interference), muscle pain (3 items; frequency, severity, interference); fatigue (2 items; severity, interference); vaginal dryness (1 item; severity); vaginal discharge (1 item; presence/absence); irregular periods/vaginal bleeding (1 item; presence/absence); nausea (2 items; frequency, severity); vomiting (2 items; frequency, severity); diarrhea (1 item; frequency); constipation (1 item; severity); decreased appetite (2 items; severity, interference); rash (1 item; presence/absence). PRO-CTCAE frequency, severity, and interference items use a 5-point Likert-type response scale respectively ranging from "never" to "almost constantly", "none" to "very severe", and "not at all" to "very much" (each scored from 0 to 4, with higher scores indicating a higher frequency, severity, or interference of the given symptomatic AE) (75). PRO-CTCAE presence/absence items use a dichotomous "no"/"yes" response scale (scored 0 and 1, respectively) (75).

In accordance with scale developer recommendations (76), conditional branching will be employed for the electronic administration of PRO-CTCAE symptom terms that have two or more items to reduce respondent burden. The logic branches from frequency, then to severity, then to interference. Using the joint pain items as an example: if a given respondent reports the frequency of joint pain is greater than "Never", the respondent will be administered the severity item; if the respondent reports severity of joint pain is greater than "None", the respondent will be administered the interference item. Using conditional branching in electronic PRO-CTCAE item administration, participants will be administered a minimum of 14 items and a maximum of 24 items, depending upon their responses.

Items from the PRO-CTCAE item library were selected in accordance with recommendations by the FDA (77, 78) and using methods informed by the published literature (79, 80).
See Section 10.10.2 (Appendix 10) for detailed item selection methods.

8.10.6 MMAS-8

The Morisky Medication Adherence Scale (MMAS-8) is a validated assessment tool used to measure non-adherence in a variety of patient populations (81). It has proved to be a valuable resource to address adherence concerns, such as forgetting to take medications or discontinuing medications without guidance. If a patient scores higher on the scale, they are evaluated as more adherent. If they score lower on the scale, they are presumed to be struggling with nonadherence. By understanding how the patient scored on the scale, clinicians and health organizations can identify underlying issues that prevent patients from taking their medications correctly, if at all.

8.10.7 PGI-S and PGI-C

The Patient Global Impression scale (PGI), also known as Subject Global Impression (SGI), is the PRO counterpart to the Clinical Global Impressions scale, (CGI), which was published in 1976 by the US National Institute of Mental Health (82). Over the years, PGI scales were used in a broad range of diseases and were modified for the purpose of clinical settings. In this study, the PGI-S and PGI-C each consist of one item based on the CGI and adapted to the current setting. The PGI-C measures change in side effects of treatment over time; while the PGI-S measures severity in side effects of treatment at the time of assessment.

8.10.8 EUROQoL EQ-5D-5L

The EQ-5D-5L is a standardized, self-rated measure of health status developed by the EuroQoL Group (83) that is designed to provide a utility score suitable for use in health economic evaluations. It provides a descriptive classification based on self-assessment of 5 domains (84): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a 5-level rating scale of no problems, slight problems, moderate problems, severe problems and extreme problems. These scores are combined to obtain discrete health states which can be assigned index values reflecting how good or bad a health state is according to the preferences of the general population of a country/region. In addition, it contains a self-rating of health on a vertical visual analogue scale from 'the best health you can imagine' to 'the worst health you can imagine' scored on a 0-100 scale. The EQ-5D-5L is available in more than 150 languages with all translations produced using a standardized translation protocol that conforms to internationally recognized guidelines (85).

9 STATISTICAL CONSIDERATIONS

9.1 POPULATIONS FOR ANALYSES

The following populations are defined (Table 6):

Table 6 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who took at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
PK population	All randomized and treated participants (safety population) with at least one post-baseline PK concentration with adequate documentation of dosing and sampling dates and times. Participants will be analyzed according to the intervention they actually received.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

9.2 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will be finalized before the first database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.2.1 General considerations

The baseline value is defined as the last available value before randomization, unless otherwise specified.

Unless otherwise specified, analyses will be performed by intervention group (and overall for baseline and demographics characteristics).

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.

- The **on-treatment period** (ie, treatment-emergent (TE) period) is defined as the period from the first IMP administration to the last IMP administration + 30 days.
- The **post-treatment period** is defined as the period from the end of the on-treatment period.

Timing of the analyses:

For each analysis, actual COD will be based on the actual date at which the minimum requirements in terms of number of events and follow-up are both met as described in the Table 7 below. Per FDA request, the second interim analysis and the final analysis should be performed when at least 2 years and at least 3 years of follow-up have been observed for all patients, respectively.

Table 7 - Timing of analyses

Analysis	Number of events required	Minimum follow-up required	Expected COD
Interim analysis 1 IBCFS	Approximately 189	-	28 months after first patient is randomized
Interim analysis 2 IBCFS	Approximately 426	2 years	48 months after first patient is randomized
Final analysis IBCFS	Approximately 568	3 years	60 months after first patient is randomized
Long-term follow-up analysis 1	-	5 years	5 years after last patient is randomized
Long-term follow-up analysis 2	-	10 years	10 years after last patient is randomized

IBCFS = Invasive breast cancer-free survival; COD = Cut-off date

9.2.2 Primary endpoint

Invasive breast cancer-free survival (IBCFS) is defined as the time 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.

A summary of the primary estimand associated with the primary endpoint is provided in Table 8.

Table 8 - Summary of primary estimand of the primary endpoint

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: to determine whether amcenestrant once a day (QD) improves the IDFS excluding second primary invasive cancers of non-breast origin (IBCFS) when compared to tamoxifen QD in patients with early breast cancer as adjuvant treatment				
Primary endpoint (Estimand 1)	IBCFS	ITT	Interruption/discontinuation of study intervention: IBCFS will be analyzed based on disease assessments irrespective of study intervention interruption/discontinuation (treatment policy strategy). Start of new therapy prior to IBCFS event: IBCFS will be analyzed based on disease assessments regardless of whether new therapy is initiated prior to event of interest (treatment policy strategy). IBCFS event documented more than 12m+90days after previous disease assessment: IBCFS will be censored at the last disease assessment prior to the event (hypothetical strategy).	One-sided log-rank test stratified by randomization stratification factors (except geographical regions), as entered in the IRT system. Hazard ratio (HR) and corresponding CI estimated using stratified Cox proportional hazard model The Kaplan Meier estimate of event free probabilities at specified time points, quartiles and corresponding 95% CI from Kaplan Meier method

Primary efficacy analysis will consist 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% will be used for statistical testing.

The primary analysis of IBCFS will be based on the following censoring rules:

- If none of the IBCFS event is observed before the IBCFS analysis COD, participants will be censored at the date of the last disease assessment documenting no IBCFS event before the COD.
- A participant without an IBCFS event and without any valid postbaseline disease assessments will be censored at the day of randomization (Day 1).
- An IBCFS event documented after more than 12 months + 90 days following randomization or the previous disease assessment, whichever is later, will be censored at the date of the last disease assessment documenting no IBCFS event prior to the documented IBCFS event or the date of randomization, whichever is later.
  Twelve months + 90 days is the longest allowed interval between visits in this trial as defined in the schedule of activities.

The HR estimates and corresponding confidence intervals will be 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 will be presented by treatment arm. The Kaplan-Meier IBCFS curves will also be provided.

Sensitivity, supportive and subgroup analyses of IBCFS will be performed as specified in the SAP.

Two interim analyses at 1/3 (approximately 189 IBCFS events, non-binding futility only) and 3/4 (approximately 426 IBCFS events, efficacy and non-binding futility) of the target number of events (approximately 568 IBCFS events) are planned. The primary IBCFS analysis corresponds either to a positive interim IBCFS analysis or the final IBCFS analysis. Detail of the interim analyses are provided in Section 9.3.

9.2.3 Secondary endpoint(s)

9.2.3.1 Key secondary efficacy endpoint

IDFS

IDFS (STEEP criteria) is defined as in the primary endpoint but including second non-breast primary invasive cancer.

A summary of the primary estimated associated with the key secondary endpoint is provided in Table 9.

Table 9 - Summary of primary estimand of the key secondary endpoint

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Key secondary objective: 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				
Key secondary endpoint (Estimand 2)	IDFS	ITT	Interruption/discontinuation of study intervention: IDFS will be analyzed based on disease assessments irrespective of study intervention interruption/discontinuation (treatment policy strategy). Start of new therapy prior to IDFS event: IDFS will be analyzed based on disease assessments regardless of whether new therapy is initiated prior to event of interest (treatment policy strategy). IDFS event documented more than 12m+90days after previous disease assessment: IDFS will be censored at the last disease assessment prior to the event (hypothetical strategy).	One-sided log-rank test stratified by randomization stratification factors (except geographical regions), as entered in the IRT system. Hazard ratio (HR) and corresponding 95% CI estimated using stratified Cox proportional hazard model The Kaplan Meier estimate of event free probabilities at specified time points, quartiles and corresponding 95% CI from Kaplan Meier method

Analysis of the key secondary endpoint analysis will consist of IDFS 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.

In order to ensure a strong control of the overall Type I error rate at a one-sided 2.5%, a hierarchical testing strategy will be used. In other words, comparison between arms on the IDFS will be performed only if the primary analysis of the IBCFS is statistically significant. Therefore, a maximum of one formal statistical comparison is planned for IDFS. Otherwise, IDFS will be analyzed descriptively as for other secondary efficacy endpoints.

Same statistical methods and censoring rules as defined for the IBCFS will be used. Sensitivity, supportive and subgroup analyses will be performed as specified in the SAP.

9.2.3.2 Other secondary efficacy endpoints

For all time to event secondary endpoints (DRFS, LRRFS, OS), the HR estimates and corresponding 95% two-sided CIs will be provided using the Cox proportional hazard model stratified by the stratification factors (except geographic region) as entered in the IRT. The time-to-event and quantiles and probabilities of being event-free at different time points (calculated using the Kaplan-Meier methods) as well as corresponding 95% CIs will be presented by treatment arm. The Kaplan-Meier curves will also be provided.

For the endpoint BCSS, the HR estimate and corresponding 95% two-sided CIs will be 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 will be presented by treatment arm. The corresponding BCSS rates and 95%CIs will be computed as "1 minus cumulative incidence function". The cumulative incidence curves will also be provided.

Sensitivity, supportive and subgroup analyses will be performed as specified in the SAP.

DRFS

DRFS is defined as the time from date of randomization to the date of the first occurrence of one of the following events:

- 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.

Same censoring rules as defined for the IBCFS will be used.

LRRFS

LRRFS is defined as the time from 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.
- Loco-regional invasive breast cancer recurrence: Invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.
- Death attributable to any cause, including breast cancer, nonbreast cancer, or unknown cause.
- Invasive contralateral breast cancer.

Same censoring rules as defined for the IBCFS will be used.

Overall Survival

Overall survival is defined as the time from date of randomization to the date of death due to any cause. In the absence of observation of death, survival time will be censored at the last date the participant is known to be alive or at the analysis cut-off date, whichever occurs first.

A summary of the efficacy endpoints analyses is provided in Table 10.

Breast Cancer-Specific Survival

Breast Cancer-Specific survival is defined as the time from randomization to the date of death attributable to breast cancer cause. Deaths attributable to nonbreast cancer cause or to unknown cause are considered competing risks at the date of death. In the absence of observation of death, survival time will be censored at the last date the participant is known to be alive or at the analysis cut-off date, whichever occurs first.

Table 10 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary	
IBCFS	Stratified logrank for statistical testing. Stratified Cox proportional hazard model for HR. Kaplan-Meier method for quantiles and probabilities of being event free at different time points.
Secondary	
Key secondary	
IDFS	Stratified logrank for statistical testing. Stratified Cox proportional hazard model for HR. Kaplan-Meier method for quantiles and probabilities of being event free at different time points.
Other secondary	
DRFS, LRRFS, OS	Stratified Cox proportional hazard model for HR. Kaplan-Meier method for quantiles and probabilities of being event free at different time points.
BCSS	Stratified Fine and Gray model for HR. Cumulative incidence function method for quantiles and probabilities of the event of interest at different time points. 1 - Cumulative incidence function method for quantiles and probabilities of being event free at different time points.
Exploratory	Will be described in the SAP.

IBCFS = invasive Breast Cancer-Free Survival; IDFS = invasive Disease-Free Survival; DRFS = Disease Recurrence Free Survival; LRRFS = locoregional recurrences-free survival; HR = hazard ratio; OS = overall survival; BCSS = Breast Cancer-Specific Survival; SAP = statistical analysis plan;

9.2.3.3 Other endpoints

Patient reported outcomes

Patient reported outcome (PRO) endpoints for the PRO objective will be analyzed in participants from the safety population. These three endpoints are:

- 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.

For each questionnaire the compliance profile over time will be summarized on the safety population (number and percentage of forms received versus expected, and number and percentage of forms evaluable versus expected) per treatment arm. Reasons for non-completion will be summarized.

Descriptive statistics on the absolute value and changes from baseline will be done for each treatment arm at each timepoint during treatment period, at EOT, and at the two post-treatment follow up visits will be summarized on the safety population. Between treatment comparisons of the change from baseline over time will be provided for these selected PRO endpoints based on the safety population who have completed the baseline and at least one post-baseline PRO assessment. No formal statistical hypothesis will be tested.

Pharmacokinetics

Pharmacokinetics analyses will be described in the SAP.

9.2.4 Tertiary/exploratory endpoint(s)

Analysis of tertiary and exploratory endpoints will be described in the SAP.

9.2.5 Safety analysis

9.2.5.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

TEAEs will be coded according to MedDRA. Adverse events will be graded according to the NCI-CTCAE v5.0. The grade will be taken into account in the summary. For participants with multiple occurrences of the same preferred term (PT), the maximum grade will be used.

Summaries will be provided for all grades combined and for Grade ≥3 (including Grade 5). Missing grades, if any, will be included in the "all grades" category.

Analysis of all adverse events

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a 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.

The AE summaries will be generated with number (%) of participants experiencing at least one event.

Deaths will also be analyzed.

9.2.5.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Analyses according to PCSA and NCI grading

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE version 5.0. In addition, for laboratory variables for which NCI-CTCAE scale is not applicable, vital signs and ECG variables, PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

Analyses according to PCSA and NCI grading will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs and ECG variables, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For laboratory variables graded by NCI-CTCAE.

- The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.
- The number (%) of participants with abnormal laboratory tests during the treatment-emergent period will be summarized by grade. When appropriate, the number (%) of participants with abnormality of any grade and with Grade 3-4 abnormalities will be provided.

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

9.2.5.3 Product complaints

Product complaints will be summarized in the safety population.

9.2.6 Other analysis

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9 (Appendix 9): Contingency measures for a regional or national emergency that is declared by a governmental agency.

9.3 INTERIM ANALYSES

Two interim analyses are planned based on the primary IBCFS endpoint at 1/3 (non-binding futility only) and 3/4 (efficacy and non-binding futility) of the planned total number of events expected. The stopping boundaries for non-binding futility are based on the observed HR based on the stratified Cox proportional hazard model, ie, an HR>1.2 for the first interim analysis and an HR>1.1 for the second interim analysis. The stopping boundaries for efficacy will be derived based on the O'Brien and Fleming α-spending function and depend on the actual number of IBCFS events observed at the time of the second interim analysis relative to the planned total number of events (568). Per FDA request, the second interim analysis and the final analysis should be performed when at least 2 years and at least 3 years of follow-up have been observed for all patients, respectively. Therefore, the second interim analysis and the final analysis will be performed when both the minimum required number of events and the minimum follow-up criteria have been met. If the actual number of IBCFS events observed at the final analysis is greater than the planned total number of events (568), the Type I error rate spent at the second interim analysis will not be recalculated based on the actual number of IBCFS events to avoid the inflation of the overall Type I error rate.

A summary of the IBCFS analyses is provided in Table 11.

Table 11 - Summary of IBCFS analyses

Analysis	Months after FPI (approx., under IBCFS HR=0.76)	Planned accrual	Number of events (under IBCFS HR=0.76)	Information fraction	Cumulative Probability to stop for futility under IBCFS HR=0.76 (false negative rate)	Cumulative Power (under IBCFS HR=0.76)	Futility boundary	Efficacy boundary
IBCFS IA 1 (non-binding futility only)	28	3738	189	1/3	0.1%		HR > 1.2	NA
IBCFS IA 2 (non-binding futility and efficacy)	47.5	3738	426	3/4	0.1%	69%	HR > 1.1	p ≤0.0096 HR[a] ≤0.7971)
IBCFS Final analysis	60	3738	568	1	10%	90%	p >0.0221 HR[a] >0.8447)	p ≤0.0221 HR[a] ≤0.8447)

a HR is provided only for information purposes. The interim and final decisions will be based on p-values.
FPI: First patient in; IA: interim analysis; HR: Hazard ratio; IBCFS: invasive breast cancer-free survival
Note: numbers have been rounded. Calculations were made using East 6.5 software.

In case of release of positive results at interim analysis, disease assessments data will continue to be collected for each patient according to the protocol (See Section 1.3) and IBCFS results will be updated at each subsequent planned analysis (non-inferential analysis only).

The statistical analysis plan will describe the planned interim analyses in greater detail.

9.3.1 EORTC independent DMC

This study will use the EORTC IDMC. The first IDMC meeting will be set up to review early safety results (eg, after approximately 100 participants have completed at least 2 cycles, or after 6 months after first participant randomized, whichever occurs first), and then periodically (eg, every 6 months) to examine the cumulative safety data, accrual and treatment exposure.

In addition to review of safety results, the IDMC will also evaluate efficacy at the two interim analyses and make a recommendation to the Study Steering Committee regarding study continuation based on observed results of the study.

Ad hoc IDMC meetings may also be held if a significant safety issue or an issue deemed important for discussion arises on this or other amcenestrant studies.

Following each meeting, the IDMC will make recommendations to the Study Steering Committee regarding the continued safety of treating ongoing and future study participants, as well as the course of action regarding the conduct of the study in compliance with the IDMC Charter.

9.4 SAMPLE SIZE DETERMINATION

For IBCFS, a total of 568 IBCFS events will be needed to reject the null hypothesis using a log-rank test at the one-sided level of 2.5% and 90% power under the assumption of an HR of 0.76. Assuming proportional hazards under an exponential model and based on an anticipated 4-year IBCFS rate of 82% in the tamoxifen arm, this is expected to correspond to a 4-year IBCFS rate of 86% in the amcenestrant arm.

Based on a piecewise enrollment assumption over 24 months as described in Table 12, an IBCFS cut-off date (COD) 60 months after the first participant randomized and an annual dropout rate of 1%, a total of 3738 participants are expected to be randomized in a 1:1 ratio into the amcenestrant and tamoxifen arms.

Table 12 - Piecewise enrollment assumptions

Month	Cumulative enrollment (%)
3	5%
6	15%
12	40%
24	100%

The number of events/sample size calculation accounts for two interim analyses at 1/3 (non-binding futility only) and 3/4 (efficacy and non-binding futility) of the planned total number of events (Section 9.3).

Comparison between treatment arms on IDFS will be performed only if statistical significance has been achieved for IBCFS. Therefore, formal comparison on IDFS will be performed either at the second interim analysis or at the final analysis of IBCFS. Therefore, the number of IDFS events observed will depend on the occurrence of second non-breast primary invasive cancer and will therefore be at least equal to the number of IBCFS events.

Calculations were made using East 6.5 software.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Trial organization

AMEERA-6 is an industry sponsored trial, conducted in partnership between SANOFI, the Breast International Group (BIG), the European Organization for Research and Treatment of Cancer (EORTC) and Alliance Foundation Trials (AFT), and academic research groups from the BIG and the US networks.

SANOFI is the Sponsor of the trial, and will provide funding, the investigational drug (amcenestrant) and the placebos for the trial.

BIG is responsible of the conduct of the study within the BIG network, with EORTC leading the protocol development, the study management, and data analysis activities, as well as the medical monitoring, and AFT managing the study in the United States. Sanofi conducts the study in selected countries outside the geographical scope of the academic networks and oversees the global conduct of the trial.

The protocol has been developed in collaboration between all four study partners, and subject to the approval by the Study Steering Committee.

10.1.2 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator's Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
    - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as “substantial” (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.3 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, Sponsor must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF (see Section 5.4). However, in case the participant is a temporary screen failure, there is no need to have participant reconsent (ie, new ICF signed) if the participant finally participates in the trial.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9 (Appendix 9): Contingency measures for a regional or national emergency that is declared by a governmental agency.

10.1.5 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

"Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals)". They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.

- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies' disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.6 Committees structure

The study will be governed by the Steering Committee (SC), which will be the ultimate decision-making body of the Study. The SC charter shall stipulate the composition as well as the working rules of the SC. The SC will be composed of representatives from the Sponsor (SANOFI) as well as representatives from the academic research groups (BIG, EORTC, AFT).

The Executive Committee (EC) which is a subset of the SC, will serve to facilitate the work of the SC, to respond to questions of the JSMT and the IDMC, and report to the SC.

The Joint Study Management Team (JSMT) will be responsible for the daily conduct of the Study, shall report to the Steering Committee and the Executive Committee and shall execute the decisions of both these committees.

The Translational Advisory Committee (TAC) shall be the expert body which functions under the governance of the SC. It provides guidance to the SC on optimal use of study data and/or biological samples outside the protocol, and recommends to the SC for final approval, according to the Policy for Access to Study Data and Biological Samples.

The SC, EC, JSMT and TAC composition, responsibilities and working procedures, will be described in the specific charters developed for the study.

The independent data monitoring committee (IDMC) will be in charge of the independent oversight of this study. The composition of the IDMC is described in EORTC Policy "Independent Data Monitoring Committees for EORTC studies" (EORTC POL004, accessible on EORTC website) and its functioning is ruled by the charter annexed to the Policy. The IDMC membership, data to be reviewed, timing of the planned reviews as well as the operating procedures will be described in the IDMC charter.

10.1.7 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following the mutually agreed by the Study partners specific Publications and Presentations Policy developed for the study to ensure accuracy, fair balance in authorship and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request according to the study-specific Policy for Access to Study Data and Biological Samples.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access will be described in the specific dedicated Policy for Access to Study Data and Biological Samples developed for the study.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Implementation of Drug Clinical Trial Information Registration and Disclosure" ("Notification No. 28"), requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations".

10.1.8 Data quality assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or Sponsor's representatives electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined in the relevant study plans to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or Sponsor's representatives is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site termination

The Steering Committee reserves the right to close the study site or terminate the study at any time for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Steering Committee, as well as reasons for the early closure of a study site by the Steering Committee or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

10.1.11 Publication policy

- Publications and oral presentations of any aspects from the study including study design and study results shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the specific dedicated Publications and Presentations Policy developed for the study. This policy will be made available to all investigators/sites and groups participating in the study.
- The publications of the main trial results and any other related study publications will be written by the Study SC Chairs or others as applicable on the basis of the analysis reports performed at the EORTC Headquarters and will be sent to a major scientific journal.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 13 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 13 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	
	Blood urea nitrogen (BUN) or Urea
	Creatinine
	Glucose non-fasting
	Potassium
	Sodium
	Calcium (total calcium)
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase[b]
	Total and direct bilirubin
	Total protein
Lipids	
	Total cholesterol
	LDL-cholesterol
	HDL-cholesterol
Pregnancy testing	• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]
Other blood tests	• Follicle-stimulating hormone and estradiol (pre/perimenopausal women only) • Coagulation: PT/INR • Bone turn over markers (CTX, P1NP)[d]

NOTES:
a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 8.2.3 and Section 10.10.1 (Appendix 10). All events of Grade ≥3 ALT increase should be reported as adverse events of special interest (AESI).
b If alkaline phosphatase is elevated, consider fractionating.
c Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
d β-CTX and tP1NP(total P1NP) are not acceptable. If the local lab cannot perform CTX and P1NP then serum should be sent to a central lab.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participantswill be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participant and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events <u>meeting</u> the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
    - Intensive treatment in an emergency room or at home for:
      - Allergic bronchospasm
      - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
      - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
    - Development of drug dependence or drug abuse
    - Suicide attempt or any event suggestive of suicidality
    - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
    - Bullous cutaneous eruptions
    - Cancers diagnosed during the study or aggravated during the study

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the e-CRF.

- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representatives in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representatives. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representatives.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories, using NCI-CTCAE v 5.0.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representatives to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representatives will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representatives by telephone.
- Contacts for SAE reporting can be found in Investigator Study File.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representatives.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Investigator Study File.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

i. Premenarchal

ii. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

iii. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, or in in participants who are not using hormonal contraception or hormonal replacement therapy (HRT), confirmation with more than one FSH measurement (>34.4 IU/L for FSH and <10 pg/mL for estradiol if institutional range is not available) is required, as per local regulations. HRT must be discontinued to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE:

In addition to inclusion criteria I. 11

- Female participants of child-bearing potential:
  - Must agree to be on a gonadotropin-releasing hormone analog (to be continued while receiving the study intervention) as per label
  - Must have negative serum ß-HCG test at screening
  - Must agree to use highly effective methods of contraception during the treatment period until the end of relevant systemic exposure (ie, 5 times of the longest IMP half-life (tamoxifen) plus 6 months period, which corresponds to ~9 months for tamoxifen as per CMDh guidance (86).
  - Must not donate ova from screening until the end of the contraception period as defined above
- Male participants without prior orchiectomy:
  - Agree to be on a gonadotropin-releasing hormone analog (to be continued while receiving the study intervention) as per label and use a male condom during intercourse during study intervention until 160 days after the end of treatment period (corresponding to the end of relevant systemic exposure (ie, 5 times of the longest IMP half-life (tamoxifen) plus a further 90-day period) as per CMDh guidance (86) and should not father a child in this period. A condom is required to be used also by vasectomized men, as well as during intercourse with a male partner, in order to prevent delivery of the drug via seminal fluid.
  - Must not donate sperm from screening until the end of the contraception period as defined above.
  - Male participants should consider sperm preservation prior to beginning therapy with study IMPs, because exposure to IMP has the potential risk of testicular injury with partial or permanent infertility.
  - Male participants and male partners of female participants must wear a male condom with spermicide, in combination with a highly effective method of contraception.

Note: In case of acceptable birth control method, partner WOCBP of a male participant should use a highly effective contraception during treatment of their partner and until the end of the contraception period as defined above.

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods*. Such methods include:

- Intrauterine device.
- Bilateral tubal occlusion.
- Vasectomized partner.

- Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant).

Note: Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

** Failure rate of <1% per year when used consistently and correctly.*

The following birth control methods result in a failure rate of more than 1% per year and are not considered acceptable birth control methods when used alone in the current trial:

- Male or female condom with or without spermicide.
- Cap, diaphragm or sponge with spermicide.

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date, but may last longer according to local regulations. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date but may last longer according to local regulations. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 APPENDIX 5: GENETICS

- A genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to germline mutations linked to the treatment outcome. The genetic research will consist on the analysis of the entire exome of the patient's genome.
- DNA samples will be analyzed for the germline mutations study by whole exome sequencing.
- The samples will be analyzed to study the genetic factors involved in the response to the study intervention to understand the related conditions to the patient's outcome.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained but no longer than 15 years after the end of the study or other period as per local requirements.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Not Applicable for this study.

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable for this study.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

CHINA

For study participants enrolled from clinical sites in China, central confirmation of ER and PgR for screening eligibility will be performed (collection of the most recent archived FFPE biopsied tumor tissue samples at screening) as well as PK analysis (collection of blood sample on pre-dose D1 Cycle 2, Cycle 7, Cycle 13 and Cycle 25 using DBS and approximately 100 plasma samples aliquots kept from on C2 and/or C7 blood collection, to determine Blood/Plasma ratio).

Biological samples related to tertiary/exploratory (genetic analyses and biomarkers) endpoints will not be collected or analyzed. The impacted biological samples are:

- Collection of plasma sample for Molecular profiling in ctDNA in all study participants on predose D1 Cycle 1 and Cycle 2, and EOT in case of disease recurrence.
- Collection of blood sample for genomic DNA in all study participants on predose D1 Cycle 1.
- Collection of blood sample for future research on predose D1 Cycle 1 and Cycle 2, and EOT in case of disease recurrence.
- Collection of FFPE tissue sample at EOT in case of disease recurrence.
- Genetic analyses and biomarker research for FFPE tissue samples at screening (except that central confirmation of ER and PgR for screening eligibility will be performed).

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, and terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

The decision for each individual participant to remain and/or start in the study should be made on a case by case basis based on best Investigator medical judgment. The clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment and the evolving situation at the site (Section 5.5). However, in case new participant is eligible for the trial, the PI/site should assess the capacity to maintain these patients into the trial before any screening procedures will start. If the site cannot guarantee an accurate follow-up in the context of the trial, alternative treatment outside the clinical trial should be proposed.

Study assessments and procedures

When participants are already randomized and/or treated, attempts should be made to perform all assessments in accordance with the protocol to the extent possible.

When possible, the focus should be on Investigational Medicinal Product (IMP) administration and safety blood collection (eg, biochemistry and hematology). However, all efforts should be made to perform the measurements of key parameters for efficacy endpoints (eg, tumor assessments). The deviations from the study protocol (eg, treatment delay, omission, tests not performed) should be documented in the source document and collected in the appropriate pages of the eCRF.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, mobile applications, etc) may be planned for the collection of possible safety and/or efficacy data (eg safety assessments, efficacy assessments especially the tumor assessment, PRO).
- If onsite visits are not possible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed.
- The Direct-to-Patient (DTP) supply of the IMP from the PI/site where allowed by local regulations and agreed upon by participant. (Section 1).

Contingencies implemented due to emergency will be documented.

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs) (Section 10.1.9).

10.10 APPENDIX 10: ADDITIONAL APPENDICES

10.10.1 Recommended dose modification guidelines for study treatment-related adverse event

Recommended dose modifications of study intervention (**Amcenestrant/Amcenestrant-matching placebo, Tamoxifen/Tamoxifen-matching placebo**) are presented in Table 14.

Table 14 - Recommended dose modification or discontinuation of study treatment-related toxicities

NCI CTCAE v5 grade	Management of endocrine therapy (Amcenestrant/amcenestrant-matching placebo, Tamoxifen/tamoxifen-matching (placebo)
Toxicities	
Grade 1 or 2	No dose adjustment is required.
Grade 3 (if persisting despite optimal medical treatment)	Administer endocrine therapy if toxicity is not attributed to the IMP. If attributable, omit endocrine therapy until symptoms resolve to Grade ≤1, or Grade ≤2 (if not considered a safety risk for the patient). If resolved to Grade ≤1, or Grade ≤2 (if not considered a safety risk for the patient), resume the omitted endocrine therapy at the same dose. In case of first recurrence of the same Grade 3 event: administer at the same dose if restart is possible. In case of second recurrence of the same Grade 3 event: permanently discontinue IMP.
Grade 4	Administer endocrine therapy if toxicity is not attributed to the IMP. If attributable, omit endocrine therapy until symptoms resolve to Grade ≤1, or Grade ≤2 (if not considered a safety risk for the patient). If resolved to Grade ≤1, or Grade ≤2 (if not considered a safety risk for the patient), resume the omitted endocrine therapy at the same dose. If resolved to Grade 3: refer to Grade 3 instructions above. In case of first recurrence of the same Grade 4 event attributed to the IMP: permanently discontinue IMP.
Increase of ALT confounding factors such as, liver metastasis, hepato-biliary disorders, concomitant medications, etc. should be excluded prior to dose modifications	
Grade 0 or 1	No dose adjustment is required
Grade 2	Omit endocrine therapies administration until recovery to Grade ≤1, and then restart endocrine therapies at the same dose. In case of recurrence of the same Grade 2 event: administer at the same dose if restart is possible.
Grade 3	Omit endocrine therapies administration. Repeat LFTs within 2-3 days. If ALT levels not recovered, monitor LFTs weekly (or more frequently, if clinically indicated) until recovery to Grade ≤1 ALT increased (or baseline grade). On recovery, restart endocrine therapies at the same dose. In case of first recurrence of the same Grade 3 event: administer at the same dose if restart is possible. In case of second recurrence of the same Grade 3 event: permanently discontinue endocrine therapies.
Grade 4	Permanently discontinue study treatment

Liver function tests (LFTs) include AST, ALT, ALP (isoenzymes if Grade >2), total bilirubin (fractionated if >2 x ULN direct), GGT, and INR (if total bilirubin >2.5 ULN).
Grading according to CTCAE v5.0.
NCI CTCAE v5 = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; LLN = lower limit of normal.

10.10.2 Methods for selecting items from the pro-CTCAE item library

PRO-CTCAE items chosen for this study were systematically selected from the PRO-CTCAE item library to measure 14 symptomatic AEs (representing 24 items) known to be associated with amcenestrant (as seen in the AMEERA-1 Phase 1/2 study) and/or tamoxifen (based on the USPI, EU SmPC, and/or clinician input). Items from the PRO-CTCAE item library were selected in accordance in the PRO-CTCAE with recommendations by the FDA (73, 74) and using methods informed by the published literature (75, 76). Items were eligible for inclusion if they assessed one or more attribute (frequency, severity, interference, presence/absence) of a symptomatic adverse event (AE) that:

1.) was a related TEAE that occurred in ≥ 5% of the pooled population treated with amcenestrant ≥ 150 mg QD as monotherapy in Parts A and B of the AMEERA-1 Phase 1/2 study (TED14856) (85);

2.) occurred in ≥ 10% of patients on tamoxifen for adjuvant therapy in at least study listed in the tamoxifen USPI (86);

3.) are very common (incidence of ≥1/10) in patients on tamoxifen per the tamoxifen EU SmPC (87); and/or

4.) did not meet inclusion criteria 1, 2, or 3, but were considered clinically relevant in patients on tamoxifen based on clinician input and a retrospective cohort study of the clinician- and patient-reported toxicities experienced among early breast cancer patients on AIs and tamoxifen using data from the Unicancer CANcer TOxicities (CANTO) cohort. If a symptomatic AE was eligible for inclusion based on the criteria above and the PRO-CTCAE included multiple items associated with the symptomatic AE, all items available items were included.

Table 15 presents the 14 symptomatic AEs (representing 24 items) selected for assessment from the PRO-CTCAE item library, the attributes assessed by the PRO-CTCAE items, the number of items assessed for each symptomatic AE, and the inclusion criteria met by each symptomatic AE.

Table 15 - Symptomatic AEs and items selected from the PRO-CTCAE item library for inclusion in EFC16133 and inclusion criteria met by each symptomatic AE

Symptomatic AE from PRO-CTCAE Item Library	Attributes assessed (number of items)	Inclusion criteria met
Hot flashes	Frequency, severity (2)	1, 2, and 3
Increased sweating	Frequency, severity (2)	4
Joint pain	Frequency, severity, interference (3)	1 and 2
Muscle pain	Frequency, severity, interference (3)	4
Fatigue	Severity, interference (2)	1, 2, and 3
Vaginal dryness	Severity (1)	4
Vaginal discharge	Presence/absence (1)	2 and 3
Irregular periods/vaginal bleeding	Presence/absence (1)	2 and 3

Symptomatic AE from PRO-CTCAE Item Library	Attributes assessed (number of items)	Inclusion criteria met
Nausea	Frequency, severity (2)	1, 2, and 3
Vomiting	Frequency, severity (2)	1 and 2
Diarrhea	Frequency (1)	1
Constipation	Severity (1)	1
Decreased appetite	Severity, interference (2)	1
Rash	Presence/absence (1)	3

10.10.3 Eastern Cooperative Oncology Group performance status scale

Assessment of ECOG/WHO PS will be assessed at the time points specified in SoA (Section 1.3).

ECOG PS (performance status) should be obtained on the scheduled day, even if study intervention is being held.

Table 16 - Eastern Cooperative Oncology Group (ECOG) performance status (PS) scale

0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

10.10.4 Abbreviated modification of diet in renal disease formula

Glomerular Filtration Rate (GFR) (mL/min/1.73 m^2) = 175 × $(SCr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if Female) × (1.212 if African-American).

Abbreviation: SCr = Serum creatinine in mg/dL; Age in years

10.11 APPENDIX 11: ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
AI:	aromatase inhibitor
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ASCO:	American Society of Clinical Oncology
AST:	aspartate aminotransferase
AUC:	area under the curve
BCSS:	breast cancer-specific survival
BID:	twice daily
BMD:	bone mineral densitometry
BOR:	best overall response
CBR:	clinical benefit rate
CDK4/6:	cyclin-dependent kinase 4 and 6
CI:	confidence interval
COA:	clinical outcomes assessment
CONSORT:	Consolidated Standards of Reporting Trials
CYP:	cytrochrome P450 enzymes
DBS:	dried blood spot
DDI:	drug-drug interaction
DFS:	disease free survival
DNA:	deoxyribonucleic acid
DRFS:	distant recurrence-free survival
DTP:	direct to patient
DVT:	deep vein thrombosis
DXA:	dual-energy X-ray absorptiometry
ECG:	electrocardiogram
eCOA:	electronic clinical outcomes assessment
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
EDC:	electronic data capture
eGFR:	estimated glomerular filtration rate
EORTC:	European Organization for Reasecrh And Treatment of Cancer
EOT:	end of treatment
EQ-5D-5L:	EuroQoL Questionnaire with 5 Dimensions and 5 Levels per Dimension
ER:	estrogen receptor
ESR1:	Estrogen receptor gene
EU:	European Union
FACT GP5:	Functional Assesssment of Cancer Therapy - Item GP5
FDA:	Food and Drug Administration
FFPE:	formalin fixed paraffin embedded
FIH:	first-in-human
FPI:	first patient in

FSH:	follicle stimulating hormone
gDNA:	genomic deoxyribonucleic acid
GGT:	gamma-glutamyl transferase
GHQ:	global health status/quality of life
HCV:	hepatitis C
HER2:	human epidermal growth factor receptor 2
HR:	hazard ratio
HR+:	hormone receptor positive
HRQL:	health-related quality of life
HT:	hormonal therapy
IA:	interim analysis
IB:	investigator brochure
IBCFS:	invasive breast cancer-free survival
ICF:	informed consent form
IDFS:	invasive disease-free survival
IEC:	Independent Ethics Committee
IES:	intergroup exemestane study
IHC:	immunohistochemistry
IM:	intramuscular
IMP:	investigational medicinal product
INR:	international normalized ratio
IRB:	Institutional Review Board
ITT:	intent-to-treat
LFT:	liver function test
LHRH:	luteinising hormone releasing hormone
LRRFS:	loco-regional relapse-free survival
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
MMAS:	Morisky medication adherence scale
MRI:	magnetic resonance imaging
NCI-CTCAE:	National Cancer Institute-Common Terminology Criteria for Adverse Event
NMPA:	National Medical Products Administration
ORR:	objective response rate
OS:	overall survival
P1NP:	Procollagen type I N-terminal propeptide
PCSA:	potentially clinically significant abnormalities
PD:	progressive disease
PO:	oral
PR:	partial response
PRO:	patient-reported outcome
PRO-CTCAE:	patient-reported outcomes version of the common terminology criteria for adverse events
PT:	preferred term
QD:	once a day
QLQ BR23:	EORTC quality of life questionnaire - Breast cancer specific module
QLQ C30:	EORTC core quality of life questionnaire version 3

RNA:	ribonucleic acid
RR:	relative risk
SAP:	statistical analysis plan
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2
SERD:	selective estrogen receptor degrader
SERM:	selective estrogen receptor modulator
SmPC:	summary of product characteristics
SoA:	schedule of activities
STEEP:	standardized definitions for efficacy endpoints in adjuvant breast cancer trials
SUSAR:	suspected unexpected serious adverse reaction
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
UGT:	uridine 5'-diphospho-glucoronosyltransferase
ULN:	upper limit of normal

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

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