AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**Phase 2 window study of two dose levels of amcenestrant [SAR439859] (SERD) versus letrozole in newly diagnosed pre-operative post-menopausal patients with ER positive, HER2 negative primary breast cancer**
Protocol number:	**ACT16106**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR439859 (amcenestrant)**
Study phase:	**Phase 2**
Short title:	**Phase 2 window study of amcenestrant (SAR439859) versus letrozole in post-menopausal patients with ER+, HER2- pre-operative primary breast cancer (AMEERA-4)**
Sponsor name:	**Sanofi Research and Development**
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	Manufacturer: Sanofi

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 02	All	04 Feb 2021, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01	All	20 Jan 2020, version 1 (electronic 1.0)
Original Protocol	All	28 Jun 2019, version 1 (electronic 1.0)

Amended protocol 02 (04 Feb 2021)

This amended protocol (amendment 02) 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.

OVERALL RATIONALE FOR THE AMENDMENT

The objectives of this amendment are to

1. Incorporate mandated Clinical Trial Facilitation Group (CTFG) guidance to clarify the requirement of FSH measurements to confirm postmenopausal status;
2. Include contingency measures for a regional or national emergency, as declared by a governmental agency;
3. Update the inclusion/exclusion criteria, prohibited concomitant medications and AESI according to the new available data from ongoing amcenestrant studies;
4. Optimize the PK assessment time points for amcenestrant.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SOA): notes of FSH test & 5.1 Inclusion criteria I04 b)	Updated the protocol verbiage to reflect serial FSH measurements are required to confirm postmenopausal status for the patients who have received hormonal replacement therapy but have discontinued this treatment and in the absence of amenorrhea >12 months.	In line with the recommended Clinical Trial Facilitation Group (CTFG) guidance dated 2014, multiple FSH measurements (at least two) to confirm postmenopausal state should be conducted before including women in the absence of amenorrhea >12 months.
1.3 Schedule of Activities (SOA): footnote d; & 8.6.1 Tumor biopsy Section 8.8.1 Protein Biomarkers	Added Cyclin D1 in the exploratory protein biomarker panel to be tested by IHC in tumor tissues.	To complement data on impact of amcenestrant and letrozole on cell cycle arrest in addition to Ki67, since Cyclin D1 is regulated by ER.
3 Objectives and endpoints: Table 1; & 8.6.1 Tumor biopsy	Added Complete Cell Cycle Arrest (CCCA) as an exploratory endpoint to further assess impact on proliferation; and added digital assessment of protein biomarkers.	To add some additional tools to evaluate impact on proliferation, and to explore increased reproducibility and objective measurement of protein expression.
1.3 Schedule of Activities (SOA)	Removed PK sampling on Day 1 and Day 7, and added PK sampling on Day 15.	To optimize the PK sample collection time points. So that an on-site visit could be changed to a remote visit whenever possible (especially during pandemic).
5.1 Inclusion criteria I01	Added “or country's legal age of majority if the legal adult age is >18 years old”.	To adapt some local country’s law.
1.3 Schedule of Activities (SOA) & 5.2 Exclusion criteria E01 & 10.2 Appendix 2: Clinical laboratory tests	Added hepatitis A/B/C viral serologies at screening. And updated the exclusion criterion E01 to exclude participants with known active hepatitis A/B/C, or hepatic cirrhosis.	As the study IMPs have a potential to induce hepatic toxicity, the implemented changes are added as part of risk minimization strategy.
5.2 Exclusion criteria E04 & 6.5 Concomitant therapy & 10.8 Appendix 8: List of Strong CYP3A Inducers	Updated the exclusion criterion E04 to remove treatment with moderate CYP3A inducers; updated the list of CYP3A inducer and removed moderate CYP3A inducers from it.	Availability of new data showing that no interaction is anticipated with moderate CYP3A inducers; availability of updated data from October 2020 extraction - from the DDI database of University of Washington.
5.2 Exclusion criteria – E05 & 6.5 Concomitant therapy & 10.9 Appendix 9	Removed exclusion criterion E05 - 'Treatment with strong or moderate CYP2C8 inducers within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest and cannot be replaced’. Removed the list of prohibited concomitant therapies with regards to CYP2C8 inducers from Appendix 9 and added the lists of CYP sensitive substrates.	Availability of new data showing that no interaction is anticipated with moderate CYP2C8 inducers, and there is no known strong CYP2C8 inducers. And availability of updated data from October 2020 extraction - from the DDI database of University of Washington.
5.2 Exclusion criteria E06 & 6.5 Concomitant therapy	Added BCRP substrate in prohibited concomitant medication.	To be consistent with last IB update, as amcenestrant was identified as a potential BCRP inhibitor.

Section # and Name	Description of Change	Brief Rationale
5.3 Lifestyle considerations & 6.5 Concomitant therapy	Added recommendation of using broad spectrum sunscreens filtering both the UVA and UVB light exposure.	Risk minimization strategy for photosensitivity reactions.
6.5 Concomitant Therapy	Prolonged the duration of prior treatment which must be recorded in eCRF to "from 30 days prior to randomization".	The prior treatment received within 30 days prior to randomization need to be recorded in eCRF for checking the patient's eligibility.
8.3 AEs and SAEs	Added phototoxicity reaction in AESI.	Preclinical toxicity studies using amcenestrant indicated a potential risk for phototoxicity. Therefore, photosensitivity has been added as an AESI in order to collect additional relevant information of these events.
8.3 AEs and SAEs & 6.6 Dose Modification (Table 3)	Added guidance on the management of Increase in alanine transaminase (ALT) ≥ Grade 2.	As the study IMPs have a potential to induce hepatic toxicity, the implemented changes are added as part of risk minimization strategy.
8 Study Assessment and Procedure; & 10.1.6 Data quality assurance & 10.14 Appendix 14: Contingency measures for a regional or national emergency that is declared by a governmental agency	Added new section describing the contingency measures for a regional or national emergency that is declared by a government agency.	These measures have been added to help manage the study conduct during an emergency (eg, COVID-19 pandemic).
1.1 Synopsis: primary analysis & 9.4.1.1 Analysis of primary endpoint	Changed the statistical model from t-test to analysis of covariance (ANCOVA) model.	To add baseline Ki67 as a covariate when comparing the Ki67 log-proportional change after a 14-day treatment period between treatment groups.
10.13 Appendix 13 Abbreviated modification of diet in renal disease formula	Updated the formula of eGFR calculation. Provided a linkage of eGFR calculator.	To provide site with a calculator for eGFR based on creatinine in 2 different units.
10.15 Appendix 15: Protocol amendment history	Summary of Changes in Amendment 01 was captured.	Summary of protocol history is mandated.
Throughout the Document	Added the INN name amcenestrant. And Performed administrative and editorial updates and corrections.	INN name was obtained. And to improve consistency and clarity.
Throughout the amended protocol	Performed administrative and editorial updates and corrections.	To improve consistency and clarity.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: **Phase 2 window study of two dose levels of amcenestrant [SAR439859] (SERD) versus letrozole in newly diagnosed pre-operative post-menopausal patients with ER positive, HER2 negative primary breast cancer**

Short title: **Phase 2 window study of SAR439859 (amcenestrant) versus letrozole in post-menopausal patients with ER+, HER2- pre-operative primary breast cancer (AMEERA-4)**

Rationale:

Short pre-surgical trials (also known as “window” trials) are non-therapeutic studies in which patients are treated for 2 to 3 weeks immediately after their diagnostic biopsy and before breast surgery (1). Biomarkers of cellular activity (Ki67) and/or drug target modulation are measured in intraoperative biopsies and/or the surgical specimen.

Short-term preoperative ‘window’ studies of 2-3 weeks treatment are 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 (1, 2). The principle is to have access to tumor tissue before, under and after treatment for pharmacodynamic assessment and correlative studies thus providing critical insight into the optimal patient population, differences in activity between agents, influence of the tumor biology on sensitivity, and molecular mechanisms of response or resistance (1).

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 (3, 4). Although Ki67 measurements in preoperative trials cannot replace the need for adjuvant trials with clinical endpoints, they can be highly instructive in selecting or rejecting candidate approaches for Phase 3 studies and defining the most appropriate patient populations.

The purpose of this short term preoperative study is to evaluate the pharmacodynamic (anti-proliferation) activity of two dose levels of amcenestrant, a potent, orally bioavailable, and selective estrogen receptor (ER) inhibitor that belongs to the selective estrogen receptor degrader (SERD) class of compounds, in comparison with letrozole. amcenestrant antagonizes the binding of estradiol to ER and promotes the transition of ER to an inactive conformation that leads to up to 98% receptor degradation at nanomolar concentrations in cellular assays. These dual properties of amcenestrant translate to a deeper inhibition of ER pathways and a more effective anti-proliferative activity in ER-dependent breast cancer cell lines driven by mutant or wild type ER compared to fulvestrant, an approved SERD.

Amcenestrant recommended dose was established at 400 mg once daily (QD), based on the safety, pharmacokinetic (PK) and pharmacodynamic data review of the ongoing first in human study TED14856, from advanced breast cancer patients. As the patients in this study have early breast cancer, the 200 mg QD dose will also be explored.

Objectives and endpoints

Objectives	Endpoints
Primary	
To determine whether amcenestrant given at 2 different doses improves the antiproliferative activity when compared to letrozole	Change in Ki67 (percentage of positive tumor cells tested by immunohistochemistry [IHC]) after a 14-day treatment period compared to baseline assessed by central reading
Secondary	
To assess the proportion of participants with a relative decrease from baseline in Ki67 ≥50% in the three treatment arms	The proportion of participants with relative decrease from baseline in the proliferation marker Ki67 (% positive tumor cells) ≥50% as tested by IHC after a 14-day treatment period compared to baseline
To assess ER degradation in biopsies in participants in the three treatment arms	Change in ER expression measured by H-Score after a 14-day treatment period compared to baseline
To assess safety in the three treatment arms	AEs/SAEs and laboratory abnormalities

Overall design:

This is an international, prospective, open-label, Phase 2 randomized study of 2-week preoperative treatment in ER positive, human epidermal growth factor receptor (HER2) negative invasive primary breast cancer. After confirmation of eligibility criteria, postmenopausal women with early breast cancer will be randomly (1:1:1) assigned to one of the following treatment arms: amcenestrant 400 mg QD, amcenestrant 200 mg QD or letrozole 2.5 mg QD. Participants will be treated for 14 days. The surgery date should be fixed before randomization. The surgery is to be performed 1 (+1) day after the last dose of study treatment. Paired biopsies (before and after therapy) will be required for assessment of Ki67 and other biomarkers.

Disclosure Statement: This is a Parallel, Treatment study with 3 arms that is only blinded for assessors of primary endpoint.

Number of participants:

Approximately 126 patients will be randomized such that 120 evaluable participants are reached. A total of 40 evaluable participants per treatment arm are expected. Evaluable participants are defined as participants who have baseline and post-treatment available biopsies with Ki67 values. Sufficient participants will be screened to achieve 126 participants randomly assigned to study intervention.

Intervention groups and duration:

Participants will be treated with either amcenestrant 400 mg QD (dose regimen 1), amcenestrant 200 mg QD (dose regimen 2) or letrozole 2.5 mg QD, depending on the randomization allocation.

Study intervention(s)

Investigational medicinal products (IMPs)

Amcenestrant (SAR439859)

- Formulation: 100 mg capsules.
- Route of administration: PO.
- Dose regimen 1: 4 capsules QD, given in the morning, either with or without meal. Capsules should be taken approximately at the same time every day.
- Dose regimen 2: 2 capsules QD, given in the morning, either with or without meal. Capsules should be taken approximately at the same time every day.

Letrozole

- Formulation: 2.5 mg tablets.
- Route of administration: PO.
- Dose regimen: 1 tablet QD, given in the morning, either with or without meal. Tablets should be taken approximately at the same time every day.

Post-trial access to study medication: There is no access to medication post trial.

Statistical considerations:

Sample size calculations:

The sample size is determined based on the following assumptions:

- The geometric mean of percentage change in Ki67 after a 14-day treatment period for the control arm is assumed to be 70%.
- The geometric mean of reduction in Ki67 after a 14-day treatment period is increased to 85% for each amcenestrant arm. Therefore the geometric means of residual Ki67 (defined as one minus the geometric mean of reduction) are assumed to be 30% for the control arm and 15% for treatment arms, corresponding to a log fold difference of -0.693 (log(0.15)-log(0.3) under the alternative hypothesis.
- The standard deviation of the log-fold change after a 14-day treatment period is assumed to be 1.

A total of 40 evaluable participants per treatment arm will be needed to achieve 85% marginal power at the overall one-sided Type I error rate of 2.5% controlled with an Hochberg procedure, assuming a difference of at least 15% in geometric mean change of Ki67 between the control arm

and amcenestrant after a 14-day treatment period with a t-test (on the log-transformed data). The disjunctive power, ie, the probability to reject at least one null hypothesis associated with the comparison amcenestrant and the control arm, is estimated at 91.5%.

Allowing for a 5% non-evaluable participant rate, the total sample size for randomization is 126 participants (42 per treatment arm).

Primary analysis: On the assumption of a log-normal distribution, the Ki67 values will be log-transformed before analysis. The change of log (Ki67) between baseline and after a 14-day treatment period will be compared between groups using an analysis of covariance (ANCOVA) model adjusting for baseline Ki67 expression. For each group, the geometric mean of Ki67 at baseline and after a 14-day treatment period and the geometric mean of percentage reduction in Ki67 will be provided along with the 95% confidence interval. The geometric mean ratio of the proportional change between groups and associated 95% confidence interval will be provided.

Due to the multiplicity of tests as each amcenestrant dose/regimen will be compared to the control arm, a Hochberg step-up procedure will be used to control the overall one-sided Type I error rate of 2.5%.

Analysis of secondary endpoints: The proportion of participants with a relative decrease from baseline in Ki67 ≥50% between baseline and after a 14-day treatment will be provided for each treatment arm along with the 95% CI computed using the Clopper-Pearson method. The ER expression in H-score at baseline and after a 14-day treatment, as well as the change from baseline will be summarized for each group.

Analysis of safety endpoints

The observation period will be divided into 3 segments:

- The pre-treatment period is defined as the time from when the participants give informed consent to the first administration of the IMP.
- The on-treatment period is defined as the time from the first dose of IMP up to the last dose of IMP.
- The post-treatment safety follow-up period is defined as the time from the last administration of the IMP to last administration of the IMP +30 days.

Emergence will be defined during the on-treatment period only and during the period which includes both the on-treatment and post-treatment periods.

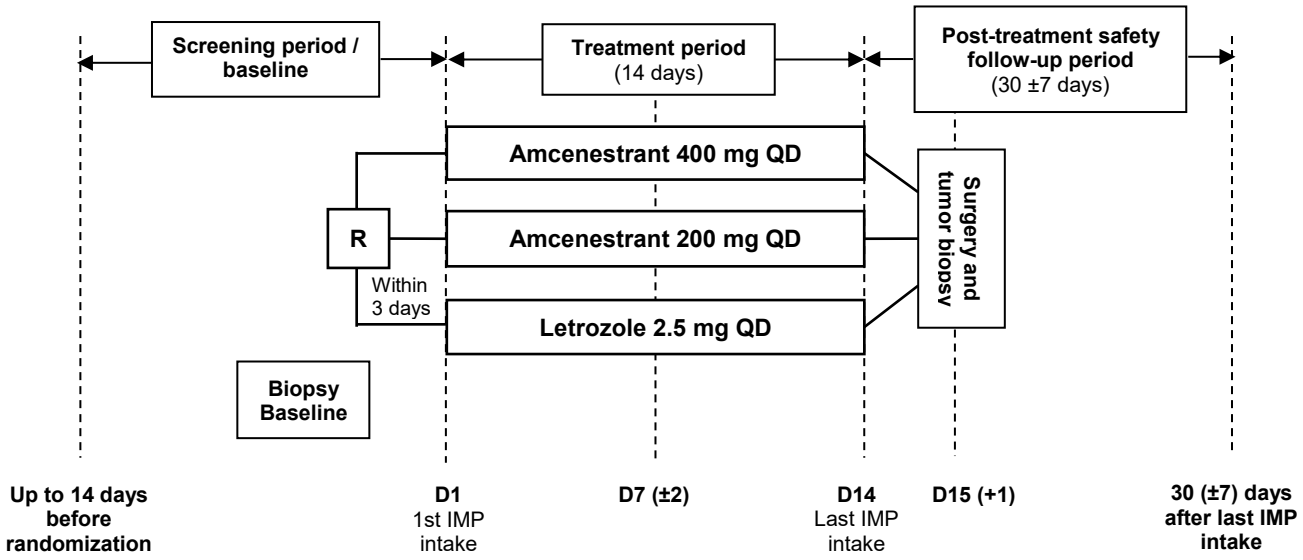
Number and percentage of participants experiencing treatment emergent adverse events (TEAEs) by Medical Dictionary for Regulatory Activities primary system organ class and preferred term will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 grade (all grades and Grade ≥3) for the safety population. Similar summaries will be prepared for treatment related TEAEs, TEAEs leading to definitive discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AEs of special interest (AESI), and AEs/serious AEs (SAEs) occurring during the post treatment period. For participants with multiple occurrences of the same AE within the treatment period, the worst grade will be used.

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 (ie, all grades and by grade) using the worst grade during the treatment period will be provided for the safety population.

Data Monitoring Committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



IMP = investigational medicinal product, QD = once daily, R= randomization

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure[a]	Screening	Treatment Period (14 days)			Surgery[c]	Post treatment safety follow-up period	Notes
	up to 14 days before randomization	D1[b]	D7 (±2)	D14	D15 (+1)	30 (±7) days after last IMP intake	
Informed consent	X						Informed consent (including genetic sampling) may be signed more than 14 days prior to randomization.
Inclusion and exclusion criteria	X						Recheck clinical status before randomization, and before 1st dosing of IMP if 1st dosing and randomization are not on the same day. See Section 5.1 and Section 5.2 for details.
Randomization	X						To take place once the consented participant has completed all the necessary screening procedures and is deemed eligible for study entry by the Investigator or designee and has already a breast conservative surgery scheduled per protocol timing requirement. All eligible participants must be randomized using IRT. Participants will be randomized within 3 days prior to first dosing of IMP. See Section 6.3 for details
Demography	X						Demography includes age, year of birth, gender, race, ethnicity.
Follicle stimulating hormone (FSH) test	X						Serial FSH measurements (at least 2) with at least 1-day interval between the measurements are required to confirm postmenopausal status for the patients who have received hormonal replacement therapy but have discontinued this treatment and in the absence of amenorrhea >12 months. FSH level in the postmenopausal range assessed prior to screening can be used as the first FSH measurement.
Full physical examination including height / weight / ECOG PS	X	(X)		X		X	Height will only be assessed at screening. Other assessments will be repeated within 1 day prior to the first dosing of IMP if abnormal or if screening assessment >7 days of D1. See Section 8.2.1 for details.
Past and current medical conditions	X						Including previous and ongoing medications, prior anticancer therapies, disease history.

Procedure[a]	Screening	Treatment Period (14 days)			Surgery[c]	Post treatment safety follow-up period	Notes
	up to 14 days before randomization	D1[b]	D7 (±2)	D14	D15 (+1)	30 (±7) days after last IMP intake	
Laboratory assessments	X	(X)		X			Standard hematology, clinical chemistry and coagulation panels. These assessments will be repeated within 1 day prior to the first dosing of IMP if abnormal or if screening assessment >7 days of D1. See Section 10.2 for details.
Viral serologies	X						Viral serologies include hepatitis A antigen or IgM hepatitis A antibody, HBs antigen or hepatitis B viral DNA, hepatitis C antibody or quantitative hepatitis C viral (HCV) ribonucleic acid (RNA).
Single 12-lead ECG	X						See Section 8.2.3 for details.
Triplicate ECG		X		X			Electronic records of triplicate ECG are required at pre-dose on D1 and at pre-dose and 3h post-dose on D14. See Section 8.2.3 for details.
Vital signs	X	(X)	X	X			These assessments will be repeated within 1 day prior to the first dosing of IMP if abnormal or if screening assessment >7 days of D1. See Section 8.2.2 for details.
Patient diary distribution		X					
Patient diary review			X	X			
Amcenestrant administration 400 mg QD		Continuous once a day (QD)					Study treatment should be taken in the morning. Study treatment duration is planned for 14 days, and should not exceed 14 days. IMP will be dispensed at the study site visits on D1. On D1 and D14, IMP will be taken on-site after fasting tests and pre-dose assessment. See Section 6.1 for details.
Amcenestrant administration 200 mg QD		Continuous once a day (QD)					
Letrozole administration		Continuous once a day (QD)					

Procedure[a]	Screening	Treatment Period (14 days)			Surgery[c]	Post treatment safety follow-up period	Notes
	up to 14 days before randomization	D1[b]	D7 (±2)	D14	D15 (+1)	30 (±7) days after last IMP intake	
Tumor Biopsy[d]	X				X		Participant selection is based on the biopsy at diagnosis analyzed in a local lab. A new core-cut biopsy (baseline sample) should be performed prior to the first dosing of IMP, as well as a core-cut biopsy from surgery specimen or new core-cut biopsy after the last IMP intake for study purpose. Alternatively, tissue from the diagnostic biopsy may be used for the baseline sample if certain criteria are fulfilled. Baseline and post-treatment biopsy will be centrally examined. See Section 8.6.1 for details.
Tumor size by ultrasound	X			X			Measurement of tumor size using ultrasound at screening (baseline) and on D14. At screening, tumor size assessed by ultrasound will also be used for inclusion criteria. See Section 8.1.2 for details.
Pathological tumor (pT) stage, the pathological node (pN) stage, pCR and ECOG response assessment, Preoperative Endocrine Prognostic Index (PEPI)					X		Pathological tumor (pT) stage, the pathological node (pN) stage, and pCR results will be collected from the local pathologist's report following examination of tissue (breast and nodes) removed at the time of surgery and reported in eCRF. ECOG response will be assessed by the investigator according to ECOG response criteria. See Section 8.1.1 and Section 8.1.3 for details.
AE/SAE review	←==========				==========	==========→	AEs of new onset as well as worsening of baseline signs and symptoms are to be reported from the signing of the informed consent to 30 (±7) days following the last IMP intake. All SAEs, and non-serious AEs of special interest, and non-serious AEs related to IMP still ongoing at the post treatment safety follow-up visit, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. See Section 8.3 for details.
Concomitant medication	←==========				==========	==========→	The period of collection of concomitant medications extends from the signing of the informed consent to 30 (±7) days following the last IMP intake. See Section 6.5 for details.

Procedure[a]	Screening	Treatment Period (14 days)			Surgery[c]	Post treatment safety follow-up period	Notes
	up to 14 days before randomization	D1[b]	D7 (±2)	D14	D15 (+1)	30 (±7) days after last IMP intake	
Genetic sample (plasma for cfDNA)		X		X			cfDNA sample collected on D1 and D14. See Section 8.7 for details.
Genetic sample (saliva for reference DNA)		X					Saliva will be collected on D1 to extract DNA which will be used as a normal reference for the mutation analysis. See Section 8.7 for details
Genetic sample (blood for DMET genotyping)		X					Blood sample will be collected on Day 1 for amcenestrant treatment arms only. See Section 8.7 for details
Amcenestrant PK				X	X		PK sampling is planned only for amcenestrant treatment arms. D14: Pre-dose (P00), T3h post dose (P01) D15: T24h post dose (P02) after last administration of amcenestrant (D14) When PK and triplicate ECG are scheduled at the same time, PK sample will be taken just after ECG recording. Participants will take IMP on-site on days of PK sampling. See Section 8.5 for details.

AE = adverse event, cfDNA = cell free DNA, DMET = Drug metabolizing enzymes and transporters, eCRF = electronic case report form, ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status, IMP = investigational medicinal product, IRT = Interactive response technology, pCR = pathological complete response, PEPI = Preoperative Endocrine Prognostic Index, PK = pharmacokinetic, pN = pathological node, pT = pathological tumor, QD = once daily, SAE = serious adverse event

a **Procedure**: Assessments to be performed prior to study treatment administration unless otherwise indicated. Informed consent should be signed before any study specific procedures. It can be signed more than 14 days prior to randomization. Screening time indicates in which timeframe exams used to support eligibility have to be done prior to randomization. All the tests or procedures scheduled on D1 should be done at predose time unless otherwise stated.

b **D1** refers to the day the participant receives the initial dose of study treatment which will be a single administration of amcenestrant 400 mg or 200 mg QD, or letrozole 2.5 mg QD.

c **Surgery**: The date of surgery should be fixed before randomization takes place. The time between first IMP administration and surgery should be of 14 days and the last dose is planned to be taken the day before surgery. Surgery should be done 1 day after the last IMP administration; however this could exceptionally be extended to a maximum of 48h after last IMP administration. In case of a longer unexpected surgery delay (>48 hours from last IMP administration), all efforts should be done to perform a tumor biopsy no more than 48 hours of last IMP administration.

d **Tumor biopsy**: Determination of tumor characteristics (HER2 status by IHC or FISH, ER and PgR by IHC, Ki67 by IHC, etc) on the diagnostic biopsy specimen based on local laboratory results serves for participant selection. For clinical sites reporting Ki67 expression by range rather than a single value, a local re-evaluation might be requested to confirm Ki67 expression ≥15%. A fresh core-cut biopsy (baseline sample) should be collected prior to the first dosing of IMP. Alternatively, tissue from the diagnostic biopsy may be used for the baseline sample if certain criteria are fulfilled (see Section 8.6.1 for details). The baseline biopsy is recommended to be performed after the eligibility is confirmed, if possible. The baseline biopsy may be performed any time prior to the initiation of study treatment. Post-treatment core-cut biopsy should be performed on the excised tissues during surgery provided the surgery is performed on D15 (+1). If surgery is delayed for any reason, every effort should be made to perform a new tumor core-cut biopsy within 48 hours maximum after last IMP intake. Baseline and post-treatment biopsy will be centrally examined for Ki67, DNA mutation analysis, RNA expression analysis, and protein analysis (eg, ER, PgR, BCL2, CyclinD1, etc).

2 INTRODUCTION

Amcenestrant is a potent, orally bioavailable, and selective ER inhibitor that belongs to the SERD class of compounds. Amcenestrant antagonizes the binding of estradiol to ER and also promotes the transition of ER to an inactive conformation that leads to up to 98% receptor degradation at nanomolar concentrations in cellular assays. Amcenestrant is a superior and broader ER degrader than all known SERD competitors. These dual properties of amcenestrant translate in a deeper inhibition of ER pathways and a more effective anti-proliferative activity in ER-dependent breast cancer cell lines driven by mutant or wild type ER compared to fulvestrant.

Amcenestrant is currently in clinical development in metastatic breast cancer; first in human (TED14856; NCT03284957) study started in September 2017 and the dose escalation of amcenestrant single agent is completed, dose expansion is ongoing.

A detailed description of the chemistry, pharmacology, efficacy and safety of amcenestrant is provided in the Investigator's Brochure.

2.1 STUDY RATIONALE

Short pre-surgical trials (also known as "window" trials) are non-therapeutic studies in which patients are treated for 2 to 3 weeks immediately after their diagnostic biopsy and before breast surgery (1). Biomarkers of cellular activity (Ki67) and/or drug target modulation are measured in intraoperative biopsies and/or the surgical specimen. Because these studies do not have a therapeutic intent, patient safety and reasonable knowledge of the optimal drug dose are major considerations for this approach so delays and/or complications from surgery are avoided. In a review of "window" trials in >4,000 patients and in all breast tumor types, there were only two deaths related to investigational drugs, and only 1% of patients could not undergo surgery due to adverse events (1, 2).

These short-term preoperative 'window' studies are 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 (1, 2). The principle is to have access to tumor tissue before, under and after treatment for pharmacodynamic assessment and correlative studies thus providing critical insight into the optimal patient population, differences in activity between agents, influence of the tumor biology on sensitivity, and molecular mechanisms of response or resistance.

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 (3, 4). In the neoadjuvant 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 correlated with recurrence-free survival (5, 6).

Although Ki67 measurements in preoperative trials cannot replace the need for adjuvant trials with clinical endpoints, they can be highly instructive in selecting or rejecting candidate approaches for Phase III studies and defining the most appropriate patient populations.

The purpose of the proposed short-term preoperative study is to evaluate the pharmacodynamic activity of two doses of amcenestrant, a potent, orally bioavailable, and selective ER inhibitor that belongs to the SERD class of compounds in comparison with letrozole. Amcenestrant antagonizes the binding of estradiol to ER and promotes the transition of ER to an inactive conformation that leads to up to 98% receptor degradation at nanomolar concentrations in cellular assays. These dual properties of amcenestrant translate in a deeper inhibition of ER pathways and a more effective anti-proliferative activity in ER-dependent breast cancer cell lines driven by mutant or wild type ER compared to fulvestrant.

2.2 BACKGROUND

Breast cancer is the most commonly diagnosed cancer and the second leading cause of death in women (7). In the United States (US) in 2019, it was estimated 268,600 new cases of invasive breast cancer as well as 62,930 additional cases of in situ breast cancer would be reported. Approximately 41,760 women were expected to die from breast cancer in 2019 (8).

Based on data from 2008 to 2014, the 5-year relative survival of individuals with breast cancer of all stages is 89.9% (9). Although the survival of patients with early breast cancer (defined as cancers that may have spread to nearby lymph nodes but not to distant parts of the body, ie, Stages I, IIA, IIB, and IIIA) is favorable, the survival of patients with advanced metastatic breast cancer (mBC) is poor; the 5-year relative survival is 100% for Stage I, 93% for Stage II, 72% for Stage III, and 22% for Stage IV (10, 11). Both endogenous and exogenous steroid hormones such as estrogen and progesterone have been implicated in the pathogenesis of breast cancer. Clinical treatment decisions are driven by the expression of estrogen receptors (ERs), progesterone receptors and human epidermal growth factor receptor (HER2) receptor status into HER2+, ER+/HER2- and triple negative clinical subtypes. About 75% of breast cancers express estrogen receptor alpha (ERα) which is a hormone regulator transcription factor (12). ER-positive breast cancers respond well to therapy targeting ER signaling either through competitive binding of ER antagonists such as tamoxifen or by blocking the production of estrogen by aromatase inhibitors (AIs) (13).

2.3 BENEFIT/RISK ASSESSMENT

This study has no direct benefit to the breast cancer patient who is indicated for an immediate surgery with no need of neoadjuvant therapy. The aim of the study is to assess the magnitude of Ki67 decrease with amcenestrant compared to letrozole together with some other biomarkers that could be of importance for increasing our understanding of breast cancer, the selection of adjuvant therapy and potential targeted therapy in case of recurrence of the disease. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of amcenestrant may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
To determine whether amcenestrant given at 2 different doses improves the antiproliferative activity when compared to letrozole.	Change in Ki67 (percentage of positive tumor cells tested by immunohistochemistry [IHC]) after a 14-day treatment period compared to baseline assessed by central reading.
Secondary	
To assess the proportion of participants with a relative decrease from baseline in Ki67 ≥50% in the three treatment arms.	The proportion of participants with relative decrease from baseline in the proliferation marker Ki67 (% positive tumor cells) ≥50% as tested by IHC after a 14-day treatment period compared to baseline.
To assess ER degradation in biopsies in participants in the three treatment arms.	Change in ER expression measured by H-Score after a 14-day treatment period compared to baseline.
To assess safety in the three treatment arms.	AEs/SAEs and laboratory abnormalities.
Tertiary/exploratory	
To assess the pharmacokinetics (PK) of amcenestrant 400 mg QD and 200 mg QD.	Amcenestrant plasma concentrations.
To assess the complete cell cycle arrest (CCCA: Ki67 ≤2.7%) rate in the three treatment arms.	The proportion of participants achieving CCCA (Ki67 ≤2.7%) after a 14-day treatment period.
To determine the expression of additional tumor protein biomarkers (eg, BCL2, etc) and the RNA profile over time in the three treatment arms.	Change in protein expression (as measured by H-score) and in RNA expression profile on tissue sample after a 14-day treatment period compared to baseline.
To assess protein biomarkers in tumor tissues by using digital image-based methods and changes over time in the three treatment arms	Protein expression at baseline and change over time compared to baseline, by means of digital image-based method, after a 14-day treatment period.
To determine the DNA mutation profile in tumor and cell-free DNA (cfDNA) to assess a potential link with Ki67 effect.	DNA mutation profile in tumor on tissue sample and cfDNA in blood sample at baseline and after a 14-day treatment period, and change in cfDNA mutation profile after a 14-day treatment period compared to baseline.
To evaluate PK/PD relationship of amcenestrant with pharmacodynamics and/or safety.	Amcenestrant PK, biomarker expression and electrocardiogram (ECG).
To assess the Eastern Cooperative Oncology Group (ECOG) response rate in the three treatment arms.	ECOG response according to ECOG response criteria (14) (based on breast tumor shrinkage, pCR and ECOG performance status) after a 14-day treatment period.
To assess the Preoperative Endocrine Prognostic Index (PEPI) risk score of the three treatment arms.	PEPI risk score assessed after a 14-day treatment period.
To assess in participants the pathological complete response (pCR) of amcenestrant given at 2 different doses and letrozole.	The proportion of participants achieving pCR after a 14-day treatment period.

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the pharmacodynamic, PK, efficacy, safety assessments selected for this study are considered well established and relevant in an oncology Phase 2 study setting.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an international, prospective, open-label, Phase 2 randomized study of 2-week preoperative treatment in post-menopausal patients with ER positive, HER2 negative invasive primary breast cancer.

After confirmation of eligibility criteria and the date of breast conservative surgery is fixed, postmenopausal women with early breast cancer will be randomly (1:1:1) assigned to one of the following treatment arms: amcenestrant 400 mg QD, amcenestrant 200 mg QD or letrozole 2.5 mg QD. Patients will be treated for 14 days, the last dose of study treatment being taken the day before surgery. Paired biopsies (before and after therapy) will be required for assessment of Ki67 and other biomarkers.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Amcenestrant is a potent, orally bioavailable, and selective ER inhibitor that belongs to the SERD class of compounds. It antagonizes the binding of estradiol to ER and promotes the transition of ER to an inactive conformation that leads to up to 98% receptor degradation at nanomolar concentrations in cellular assays. These dual properties of amcenestrant translate in a deeper inhibition of ER pathways and a more effective anti-proliferative activity in ER-dependent breast cancer cell lines driven by mutant or wild type ER compared to fulvestrant. The primary objective of this short-term preoperative study is to evaluate the pharmacodynamic activity of two doses of amcenestrant in comparison with letrozole.

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 (3, 4). In the neoadjuvant IMPACT study, suppression of Ki67 at 2 weeks was greater with anastrozole than with either tamoxifen or the combination of anastrozole plus tamoxifen (5, 6). So Ki67 is selected as the primary endpoint of this study.

Although Ki67 measurements in preoperative trials cannot replace the need for adjuvant trials with clinical endpoints, they can be highly instructive in selecting or rejecting candidate approaches for Phase 3 studies and defining the most appropriate patient populations.

4.3 JUSTIFICATION FOR DOSE

The rationale for selecting amcenestrant 400 mg QD and 200 mg QD doses is based on the preliminary safety review of TED14856 Phase 1 study and pharmacokinetic/pharmacodynamic (PK/PD) data from advanced/metastatic breast cancer patients.

As of 29 May 2019, 16 patients have been treated with amcenestrant single agent QD in Study TED14856 Part A. These patients were treated at 20 mg (3 patients), 150 mg (3 patients), 200 mg (4 patients), 400 mg (3 patients), and 600 mg (3 patients). In this study, pharmacodynamics assessments included ^{18}F-fluoroestradiol (^{18}F-FES PET)/computerized

tomography which has been validated as an accurate method for localizing ER-expressing tumors and as a predictive assay for breast cancer endocrine therapy. The ^{18}F-FES PET results indicated an inhibition of ER binding of 88-100% in the patients treated from 150 mg to 600 mg.

No dose-limiting toxicity (DLT) has been reported at dose levels up to 600 mg QD during DLT observation period (first 28-day period). All 16 of 16 patients (100.0%) experienced at least 1 TEAE regardless of relationship. The frequently reported TEAEs were hot flush, diarrhea, constipation, and nausea in each 6 patients (37.5%), decreased appetite in 5 patients (31.3%), asthenia and fatigue in each 4 patients (25.0%), hypoaesthesia, night sweat, and arthralgia in each 3 patients (18.8%), nasopharyngitis, urinary tract infection, upper respiratory tract infection, dysgeusia, photophobia, dyspnea, cough, abdominal pain upper, vomiting, dry skin, rash, back pain, myalgia, musculoskeletal chest pain, and pain in 2 patients each (12.5%).

A total of 3 serious TEAEs have been reported in 2 patients; one patient who received amcenestrant 150 mg QD experienced Grade 3 back pain, and fatal disease progression. Another patient who received amcenestrant 600 mg QD experienced Grade 3 failure to thrive. All of these events were considered to be not related to amcenestrant.

At the time of the dose escalation analysis, a partial response (PR) was observed in 1 patient receiving 150 mg daily, stable disease (SD) in 8 patients (50%) and progressive disease in 7 patients (43.8%). The clinical benefit rate (CBR) was observed in 8 patients (50%).

Pharmacokinetic data were obtained from two Phase 1 studies: one study in healthy post-menopausal women after a single dose of 100 to 400 mg and one study mentioned above in mBC patients after repeated QD administration from 20 to 600 mg. From a total of 16 patients dosed QD repeatedly with amcenestrant in Study TED14856, a high variability of exposures was observed after the first dose (average CV >60%) and a moderate variability after repeated administrations (average CV ~ 45%). The PK profile generally showed a rapid absorption (median time to achieve maximum concentration (t_{max}) ~ 3h) followed by a biphasic elimination profile. Overall across doses, apparent volume of distribution was large (~ 120 L), and apparent systemic clearance was low (~ 14-15 L/h). Preliminary data from the single ascending dose study in healthy population (100 to 300 mg in fasted state) showed a terminal half-life around 20 h. A moderate accumulation was observed on Day 21/22 after QD administrations up to 200 mg while no accumulation was observed at higher doses. Exposure (C_{max}, AUC_{0-24h}) increases with the dose after single dose, and up to 400 mg after repeated once daily administrations, slightly less at 600 mg. When given with food, no major increase of exposure was observed (no change on C_{max} and ~ 30 % increase on AUC_{0-24h}) with a delay on t_{max} by 1 hour.

At the time of the dose escalation analyzes, a partial response was observed in 1 patient receiving 150 mg daily, stable disease in 8 patients (50%) and progressive disease in 7 patients (43.8%). In accordance to the results obtained from these three parameters, safety, ^{18}F-FES-PET scans and pharmacokinetics, the recommended dose of amcenestrant was fixed at 400 mg QD. This recommended dose was established in mBC patients, however for patients with early breast cancer, a lower dose of 200 mg QD is thought to be of interest and is being explored with the assumption that adjuvant therapy is usually 5 years and this will allow selection of the most optimal exposure to therapy.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if she has completed all phases of the study including post treatment safety follow-up visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

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 (in case bilateral breast cancer is diagnosed at the same time, only one location as per Investigator judgment will be selected for all selection and assessment criteria):

Age

I 01. Participant must be older than 18 years of age inclusive, 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. Patients with histological or cytological proven diagnosis of invasive breast adenocarcinoma

I 03. Localized breast cancer eligible for upfront breast conservative surgery or upfront mastectomy: Stage I, Stage II or operable Stage III (excludes T4) *(AJCC Cancer Staging Manual 8th edition 2017;* [15]*)*

I 04. Participants must be postmenopausal women as defined by one of the following:

a) With spontaneous cessation of menses >12 months prior to randomization.

b) Or who have received hormonal replacement therapy but have discontinued this treatment AND have FSH level in the postmenopausal range according to institutional standards (or >34.4 IU/L if institutional range is not available) prior to randomization. (Note: serial FSH measurements are required to confirm postmenopausal status in participants who are not using hormonal replacement therapy and in the absence of amenorrhea >12 months.)

c) Or with status post bilateral surgical oophorectomy.

d) Or post bilateral ovarian ablation through pelvic radiotherapy.

I 05. A breast tumor size of at least 10 mm in greatest dimension measured by ultrasound

I 06. Primary tumor must be positive:

- ER (≥1% tumor cell staining by IHC)
- HER2 non-overexpressing by IHC (0, 1+) or in situ hybridization-negative based on single-probe average HER2 copy number <4.0 signals/cell or dual-probe HER2/centromeric probe for chromosome 17 (CEP17) ratio <2 with an average HER2 copy number <4.0 signals/cell (as per the American Society of Clinical Oncology guidelines).

I 07. Ki67 level of at least 15% at diagnosis from immunohistochemistry of the tumor based on local laboratory results

I 08. ECOG performance status 0-1

Weight

I 09. Not Applicable

Sex

I 10. Female

Informed Consent

I 11. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Medical history or ongoing gastrointestinal disorders potentially affecting the absorption of amcenestrant or letrozole. Participants unable to swallow normally and to take capsules or tablets. Predictable poor compliance to oral treatment. Participants with known active hepatitis 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 or quantitative hepatitis C (HCV) ribonucleic acid (RNA) results greater than the lower limits of detection of the assay) infection; or hepatic cirrhosis.

E 02. Participant with any other cancer. Adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer or any other cancer from which the participant has been disease free for >3 years are allowed.

E 03. Evidence of metastatic spread by standard assessment according to local practice.

Prior/concomitant therapy

E 04. Treatment with strong CYP3A inducers within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest and cannot be replaced.

E 05. Deleted in Protocol Amendment 02.

E 06. Treatment with drugs that are sensitive substrates of P-glycoprotein (P-gp) (dabigatran, digoxin, fexofenadine) or of breast cancer resistance protein (BCRP) (rosuvastatin, sulfasalazine) within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longer.

E 07. Use of any investigational agent within 4 weeks prior to randomization.

E 08. Recent use of hormone replacement therapy (last dose ≤30 days prior to randomization).

E 09. Prior anti-cancer treatment is not allowed unless it was completed at least 1 year prior to inclusion into this trial.

Prior/concurrent clinical study experience

E 10. Previous systemic or local treatment for the new primary breast cancer currently under investigation (including surgery, radiotherapy, cytotoxic and endocrine treatments).

Diagnostic assessments

E 11. Inadequate hematological function including neutrophils $<1.5 \times 10^9$/L; platelet count $<100 \times 10^9$/L, hemoglobin <8.0 g/dL.

E 12. 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 13. Inadequate renal function with serum creatinine ≥1.5 × ULN or between 1.0 and 1.5 × ULN with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 as estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula (see Section 10.13 Appendix 13).

E 14. Liver function parameters with one of the following:

- Aspartate aminotransferase >1.5 × ULN
- Alanine aminotransferase >1.5 × ULN
- Total bilirubin >1.5 × ULN.

Other exclusions

E 15. 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 16. Deleted in Protocol Amendment 01.

E 17. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 18. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 19. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

E 20. 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.

Criteria added in Amended Protocol

E 21. Treatment with drugs that have the potential to inhibit UGT (uridine 5'-diphospho-glucuronosyltransferase), including but not limited to atazanavir and probenecid within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest and cannot be replaced

5.3 LIFESTYLE CONSIDERATIONS

Amcenestrant toxicity studies indicate a potential risk for phototoxicity (described in the IB). For this reason, participants should avoid direct exposure to natural or artificial sunlight during study treatment and for at least 5 days after discontinuation of amcenestrant. It is recommended to advise to wear protective clothing, lip balm, and a broad-spectrum sunscreen with high sun protection factor (eg, ≥30) to cover UVA and UVB light exposure when outdoors with frequent re-application as necessary.

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).

Individuals who do not meet the criteria for participation in this study (screen failure) should not be rescreened.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

ARM name	Amcenestrant 400 mg QD	Amcenestrant 200 mg QD	Letrozole 2.5 mg QD
Intervention name	Amcenestrant	Amcenestrant	Letrozole (Femara®)
Type	Drug	Drug	Drug
Dose formulation	Capsules for oral use	Capsules for oral use	Tablets for oral use
Unit dose strength(s)	100 mg capsule	100 mg capsule	2.5 mg tablet
Dosage level(s)	4 capsules QD, given in the morning, either with or without meal. Capsules should be taken approximately at the same time every day.	2 capsules QD, given in the morning, either with or without meal. Capsules should be taken approximately at the same time every day.	1 tablet QD given in the morning, either with or without meal. Tablets should be taken approximately at the same time every day.
Route of administration	oral	oral	oral
IMP or NIMP	IMP	IMP	IMP
Packaging and labeling	Study intervention will be provided in blisters containing capsules. Two blisters will be sealed in 1 wallet. Each wallet will be labeled as required per mandatory regulatory requirements	Study intervention will be provided in blisters containing capsules. Two blisters will be sealed in 1 wallet. Each wallet will be labeled as required per mandatory regulatory requirements	Two blisters (each blister contains 10 tablets) will be removed from the commercial box and will be added in a new box. The box and the blisters will be labeled with all mandatory regulatory requirements

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

A complete description of the IMPs and their proper handling will be provided in a Pharmacy Manual available at the Investigational Site.

1. 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.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study interventions. All study interventions 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.

3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. A written authorization for destruction will be given by the Sponsor once the study intervention reconciliation is achieved. This destruction can be performed at site depending on study intervention specificities and local requirements or study interventions can be returned to the Sponsor for destruction.

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 8.3.6).

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, allows the IMPs 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

All participants will be centrally assigned to randomized study intervention using an Interactive Response Technology (IRT). The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it. Before the study is initiated, the telephone number and call-in directions for the Interactive Voice Response System and/or the log in information and directions for the Interactive Web Response System will be provided to each site. The IRT centralized randomization system will be used to prevent the Investigators from knowing in advance the treatment assignment.

Investigational medicinal product (IMP) will be dispensed at the study visit summarized in the Schedule of Activities (SoA). Participants will be randomized within 3 days prior to first IMP dosing (Day 1).

Returned study intervention should not be re-dispensed to the participants.

Participants cannot be randomized more than once.

Methods of blinding

This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IRT system. Potential bias will be reduced by the following steps.

- Central randomization
- The treatment will not be blinded to participants and investigators but will be blinded for the assessors of the primary endpoint Ki67 (ie, histopathologists in central lab) to avoid the potential for bias.

6.4 STUDY INTERVENTION COMPLIANCE

A patient diary will be provided to all participants during treatment.

The person responsible for drug dispensing is required to maintain adequate records of the study treatment. These records (eg, product accountability and inventory forms at site level) include the date the study treatment is received from the Sponsor, dispensed to the participant and destroyed or returned to the Sponsor. The packaging batch number on the pack must be recorded on the drug accountability form.

Participant compliance will be assessed at the Day 7 visit via the patient diary and at the Day 14 visit by counting returned capsules/tablets. At the Day 14 visit, the Investigator/Clinical staff will count the number of capsules/tablets, remaining in the returned packs, and fill in the Intervention Log Form and record the dosing information on the appropriate page(s) of the eCRF. The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and intervention log forms.

On Day 1, while the participant is in the clinic, patient diary will be dispensed and the study staff will demonstrate to the participant how to record information in the patient diary. Participants will note every day the hours of amcenestrant/letrozole given PO intake. If vomiting occurred after the intake of capsules/tablets, they need to report it in the same diary. In case of an early vomiting event, the administered dose of amcenestrant/letrozole given PO should not be repeated, and the participant should be instructed not to make it up the next day and resume the treatment the next day as prescribed. This information should be recorded in the diary. The diary will then be completed by the participant each day for each dose and will be returned to the study personnel on Day 7 and at the end of study treatment. Participants who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose.

Participants will be requested to return all unused amcenestrant/letrozole given PO to the study site at the end of the study treatment for a full compliance assessment. Clinic staff will record the study medication dosing information based on information from the patient diary and the compliance assessment.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or medicine) that the participant received within 30 days prior to randomization or receives during the study must be recorded in the eCRF along with:

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) during 14-day treatment if the drug is a potential enzyme inducer or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Concomitant medication may be considered on a case-by-case basis by the Investigator.

Any medication which is considered necessary for the participant's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator, except for those listed below.

Any anti-cancer medications (other than the study treatment) and hormone replacement therapy/hormonal contraception are prohibited from the date of informed consent to the end of study treatment.

The following therapies/medications are prohibited throughout the active treatment phase for the amcenestrant treatment arms:

- The concomitant use of drugs that are strong inducers of CYP3A since they may decrease amcenestrant exposure (See Section 10.8).
- Herbal medications and food supplements including St John's Wort and genistein during treatment period since they could decrease amcenestrant exposure.
- The concomitant use of drugs that are sensitive substrates of P-gp (dabigatran, digoxin, fexofenadine) or BCRP (rosuvastatin, sulfasalazine), since amcenestrant is a potential inhibitor of P-gp and BCRP and may increase their absorption.
- The concomitant use of drugs that have UGT inhibition potential and are contraindicated with UGT substrates, including but not limited to atazanavir and probenecid, since amcenestrant is substrate of UGT1A1 and UGT1A4.

Special caution should be taken with regards to the following therapies for the amcenestrant treatment arm:

- Proton Pump Inhibitors (PPI) (ie, omeprazole): when prescribed, amcenestrant intake should be preferred with food.
- Drugs that are sensitive substrates of CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 since it may result in loss of efficacy of these agents (See Section 10.9).
- Participants should avoid direct exposure to natural or artificial sunlight during study treatment and for at least 5 days after discontinuation of amcenestrant. 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 both UVA and UVB light exposure when outdoors with frequent re-application as necessary.

Regarding the control arm of letrozole:

- Co-administration of letrozole with tamoxifen, other anti-estrogens or estrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole.
- In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and, moderately, 2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on these isoenzymes and whose therapeutic index is narrow.
- For detailed information for contraindication and drug-drug interaction of letrozole, please refer to the approved letrozole label.

6.6 DOSE MODIFICATION

If a dose of IMP is vomited or omitted, the participant should not take the dose later or 2 doses at the next planned dose, and this information has to be recorded in the patient diary and eCRF.

Investigational medicinal product dose omission is allowed in case of severe toxicity and the reason should be documented in the eCRF. Doses omitted for toxicity are not to be replaced after the 14-day treatment period or compensated at the next planned IMP intake during the 14-day treatment period.

Conditions for dose modifications are aligned in Table 3. Please refer to letrozole label information on additional specific contraindications and events requiring use precaution, and instruction of dose modification.

Table 3 - Dose modification for amcenestrant arms and letrozole arm

NCI-CTCAE grade	Dose modifications
Grade 1 or 2	No dose adjustment required except for Grade 2 alanine transferase defined as an AESI *
Grade ≥3	Amcenestrant and letrozole should be definitely discontinued. No reintroduction is allowed.

NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
* See Section 8.3

6.7 INTERVENTION AFTER THE END OF THE STUDY

There is no access to intervention after the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The IMP should be continued whenever possible. Any IMP discontinuation must be fully documented in the eCRF.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

The duration of study intervention is 14 days. Participants may withdraw from study treatment if they decide to do so, at any time and irrespective of the reason, or this may be done at the discretion of the Investigator. All efforts should be made to document the reason(s) for discontinuation and this should be documented in the eCRF. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety.

Handling of participants after definitive intervention discontinuation

If the participants withdraw from study treatment before completing 14-day period, they will be requested to get back to the study sites as per planned visit dates after discontinuation. As an example, a participant who discontinues treatment on Day 6 will come to site for planned visits on Day 7 and Day 14. All procedures pre-scheduled for these Day 7 and Day 14 visits will be performed except PK sampling and ECG. If the participants have received less than 70% of planned dose (ie, less than a total of 10 days of treatment), the breast ultrasound will not be performed either. The post-treatment core-cut biopsy sampling from surgery specimen or a new core-cut biopsy will be performed as scheduled.

All participants will be requested to participate in the post-treatment safety follow-up visit (30 [±7] days after last IMP intake).

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.

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

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at 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.
- The participant 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.

Participants who withdraw from the study intervention before Day 14 should be explicitly 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 e-CRF 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 re-randomized/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 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 Appendix 1 (Section 10.1.9).

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. If the participant fails to meet the exclusion criteria related to laboratory assessments at Screening, the laboratory assessments may be performed one more time to assess eligibility.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Additional safety tests (eg, ECG, hematology, coagulation, and clinical chemistry) can be performed whenever clinically indicated.
- The date of surgery should be fixed before randomization takes place. The time between first IMP administration and surgery should be of 14 days. Surgery should be done 1 day after the last IMP administration; however this could exceptionally be extended to a maximum of 48 hours after the last IMP administration. In case of a longer unexpected surgery delay (>48 hours from last IMP administration), all efforts should be done to perform a tumor biopsy no more than 48 hours of last IMP administration.
- The IMP dose will be taken on-site after fasting tests and pre-dose assessment on Day 1 and Day 14.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 14: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

8.1 EFFICACY ASSESSMENTS

8.1.1 Pathological complete response

Pathological Complete Response (pCR) results will be collected from the local pathologist's report following examination of tissue (breast and nodes) removed at the time of surgery and reported in eCRF.

pCR is defined as ypT0N0 or ypTisN0: No histologic evidence of invasive tumor cells in the surgical breast specimen and axillary nodes after neoadjuvant treatment. (Eighth Edition AJCC Cancer Staging Manual; [15]).

8.1.2 ECOG response

Eastern Cooperative Oncology Group (ECOG) response is to be measured according to ECOG response criteria (14) (based on breast tumor shrinkage, pCR and ECOG performance status) by the investigator after a 14-day treatment period.

Tumor size will be measured using breast ultrasound at screening and on Day 14. At screening, tumor size assessment will be used for inclusion criteria and baseline value.

See Appendix 11 (Section 10.11) for details.

8.1.3 Preoperative Endocrine Prognostic Index (PEPI)

PEPI score will be assessed after a 14-day treatment period. The assessment includes relapse-free survival (RFS) risk score and breast cancer specific survival (BCSS) risk score.

The total PEPI score is the sum of the risk points derived from the pathological tumor (pT) stage, the pathological node (pN) stage, Ki67 levels and ER status (Allred score) of the surgical specimen. The pT and pN will be assessed locally. The Ki67 and ER status will be assessed centrally.

See Appendix 12 (Section 10.12) for details.

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 complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (at screening only) and weight will also be measured and recorded.
- Performance status as measured by the ECOG (Appendix 10 [Section 10.10).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

- Temperature, pulse rate, and blood pressure will be assessed at the time points defined in the SoA (Section 1.3).

8.2.3 Electrocardiograms

- Standard 12-lead ECGs are recorded after at least 10 minutes in supine position using an electrocardiographic device.

- Single 12-lead ECGs (safety ECGs) will be recorded at screening (locally assessed).
- Triplicates (3 12-lead ECGs) will be recorded within 5 minutes with at least 1 minute between 2 replicates on Day 1 and Day 14 in accordance with the SoA (Section 1.3), and can be repeated as clinically indicated.

  Each ECG consists of a 10-second recording of the 12 leads simultaneously, leading to:

  A single 12-lead ECG (25 mm/s, 10mm/mV) printout with heart rate, PR, QRS, QT, QTc automatic correction evaluation (by the ECG device), including date, time and number of the participants, signature of the research physician, and at least 3 complexes for each lead. The Investigator's medical opinion will be recorded in the eCRF. This printout will be retained at the site. ECGs will also be digitally stored to enable further reading by an ECG Core laboratory.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, and document this review.
  - 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.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management (eg, SAE or leading to dose modification), then the results must be recorded in the eCRF.
  - Liver function tests Grade ≥3 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. 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 notified if it is not considered to be related to the underlying disease.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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 occurring in a female 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 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 has to be reported as a standard AE.
- Increase in alanine transaminase (ALT) ≥ Grade 2.
  - Liver function tests 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 increase in ALP ≥ Grade 3), total bilirubin (direct bilirubin if total bilirubin >2 × ULN), GGT, and INR (if total bilirubin >2.5 × ULN).
  - Discontinue study intervention in case of increase in ALT ≥ Grade 2 if still on treatment, and repeat Liver function tests (LFTs) within 2-3 days. If not recovered, monitor LFTs weekly until recovery to Grade ≤1 (or baseline grade). Confounding factors such as, hepato-biliary disorders, concomitant medications, etc. should be excluded prior to study treatment discontinuation.
  - An ultrasound or other imaging in liver should be considered based on the clinical presentation.
  - A consultation with a hepatologist should be undertaken if there is,
    - unexplained or persistent increase in ALT ≥ Grade 3 despite study treatment discontinuation.
    - 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, taking into account the local and national recommendations.
- Photosensitivity
  - If photosensitivity reaction 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 discontinuation of amcenestrant. In case of amcenestrant discontinuation because of photosensitivity reaction, study participant should be followed for possibility of development of other manifestations of phototoxicity such as photo-onycholysis, lichenoid reaction or actinic granuloma.

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

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 7).

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 informed consent form (ICF) until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee 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. All SAEs, and non-serious AEs of special interest (as defined in Section 8.3), and non-serious AEs related to IMP still ongoing at the pre-specified study end-date, 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 given 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.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adverse events that are considered expected will be specified in the reference safety information.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in females will be collected after the signing the ICF until outcome of pregnancy (See Appendix 4 [Section 10.4]).
- 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).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 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 TREATMENT OF OVERDOSE

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose (as defined in Section 8.3), the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until IMP can no longer be detected systemically (at least 7 days for amcenestrant and 5 times the half life time of letrozole from the date of overdose).

3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document appropriately in the CRF.

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

8.5 PHARMACOKINETICS

- Pharmacokinetic sampling is planned only in participants randomized in amcenestrant treatment arms.
- Blood samples of approximately 1 mL will be collected for measurement of plasma concentrations of amcenestrant as specified in the SoA (Section 1.3) using a validated liquid chromatography-mass spectrometry/mass spectrometry assay. Instructions for the collection and handling of PK samples will be provided by the Sponsor in the laboratory manual.
- Samples will be used to evaluate the PK of amcenestrant. Samples collected for analyses of amcenestrant plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- It is of utmost importance to collect all blood samples at the specified time windows and according to the specifications (refer to the laboratory manual).
- Samples missed or lost for any reason should be recorded. Actual dates and times (24-hour clock time) of blood collection should be recorded. Actual dates and times of previous drug administration should also be precisely recorded.

For the comfort of the participants, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6 PHARMACODYNAMICS

Ki67 is a marker of cellular proliferation and has shown value as a predictor of benefit from treatment and of long-term outcome. Change in Ki67 is the primary endpoint. Ki67 will be evaluated in tumor tissue by IHC (See Section 8.6.1 for details). Ki67 index will be recorded independently by 2 histopathologists blinded to treatment allocation.

For additional parameters, please see Section 8.7 and Section 8.8.

8.6.1 Tumor biopsy

Determination of tumor characteristics (HER2 status by IHC or FISH, ER and PgR by IHC, Ki67 by IHC, etc) on the diagnostic biopsy specimen based on local laboratory results serves for participant selection. For clinical sites reporting Ki67 expression by range rather than a single value, a local re-evaluation might be requested to confirm Ki67 expression ≥15%.

During the study, tumor biopsy will be performed at the time points described in SoA (Section 1.3), and the assessment window is not impacted by dose omission. Biopsy samples will be examined for Ki67, DNA mutation analysis, RNA expression analysis, and protein analysis (eg, ER, PgR, BCL2, Cyclin D1) in central laboratory. Ki67 index will be recorded independently by 2 histopathologists blinded to treatment allocation. Complete Cell Cycle Arrest (CCCA: Ki67 ≤2.7%) will be evaluated. Additional protein expression assessments by digital method will be performed for some biomarkers (eg, Ki67).

- A fresh core-cut biopsy sample will be collected prior to the first dosing of IMP serving as baseline value. It is recommended that the baseline biopsy should be performed after the eligibility is confirmed, if possible. The baseline biopsy may be performed any time prior to the initiation of study treatment. Alternatively, biopsy tissue from the diagnostic biopsy may be used as baseline sample if the following criteria are fulfilled:
  - There is sufficient material available for biomarker analysis (a minimum of 7 x 5-µm sectioned FFPE slices on slides are required); AND
  - Diagnostic biopsy performed within 4 weeks prior to randomization; AND
  - No hormone replacement therapy (HRT) administered from 30 days prior to diagnostic biopsy till screening; AND
  - No anticancer treatment administrated between diagnosis and screening.
- Post-treatment core-cut biopsy samples will be collected on the excised tissues during surgery. The surgery should be performed on Day 15 (+1). If surgery is delayed for any reason, every effort should be made to perform a new tumor core-cut biopsy within 48 hours maximum after last IMP dose. If a new tumor core-cut biopsy within 48 hours maximum after last IMP dose is not performed, nevertheless it is recommended to collect post-treatment core-cut biopsy samples on the excised tissues during the planned surgery. Post-treatment biopsy samples should be collected in the same area as for baseline biopsy as far as possible.

For both the baseline pre-treatment and the post-treatment biopsy samples, a tissue block is preferred for the central analysis. If tissue sections are provided instead, it is preferred to have approximately at least 9 x 5-µm and 5 x 10-µm sections on slides, though a smaller number of slides for the baseline sample are acceptable, if necessary (see above for minimum requirement).

Pre-treatment and post-treatment biopsy samples will be fixed in neutral-buffered formalin for 24-72 hours prior to processing and embedding at local pathology centers. These biopsy samples will be sent for analyses to a central laboratory.

8.7 GENETICS

Genetic analysis of tumor biopsies and cell-free DNA (cfDNA) will be performed in this study.

Cancer gene mutations present in the tumor prior to treatment might influence the response to amcenestrant. The presence of gene mutations in tumor DNA may be assessed through

A) Mutation analysis of DNA isolated from a tumor biopsy, and
B) Mutation analysis of cfDNA isolated from plasma.

Both biopsies and cfDNA samples will be collected pre-treatment and post treatment. These analyses will focus on genes that may increase understanding of disease subtypes, the biology of cancer and related conditions, how the body handles amcenestrant, and drug response and toxicity, and possibly to identify new drug targets or biomarkers.

In addition, saliva will be collected pre-treatment as a source of normal reference DNA for comparison with the tumor-derived DNA data. Sequencing may be performed on the DNA from the saliva sample. In the event of technical issues affecting the sample, a replacement genetic saliva DNA sample may be requested from the participant.

At the study visit as specified in the SoA (Section 1.3), a blood sample will be collected only in amcenestrant treatment arms to investigate allelic variants of drug metabolizing enzymes (for example variants of UGT1A1 and UGT1A4), drug transporters and/or other ADME related genes as intrinsic factors associated with PK or PD variability of amcenestrant. This sample will be used for this specific analysis and not for other future research.

Special procedures for collection, handling, storage, and shipment will be described in a separate laboratory manual which will be available at the investigational site.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable additional analysis of DNA biomarkers to increase understanding of amcenestrant and/or cancer or related diseases, and potentially to identify new drug targets or biomarkers.

See Section 10.5 (Appendix 5) for Information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.8 BIOMARKERS

Several tumor biomarkers are evaluated in this study. For more information on DNA biomarkers, see Section 8.7 of the protocol.

8.8.1 Protein biomarkers

The expression of several proteins in the tumor will be assessed by IHC of biopsy tissue collected pre-treatment and post-treatment. These proteins may include estrogen receptor (ER), the progesterone receptor (PgR), Ki-67, B-Cell Lymphoma 2 (BCL2), Cyclin D1, and potentially

other proteins related to cancer or the activity of amcenestrant. These studies will be conducted by a central IHC lab.

These studies will increase the understanding of the activity of amcenestrant and may increase our knowledge of cancer or related conditions.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarkers related to amcenestrant or cancer, or to develop methods, assays, prognostics and/or companion diagnostics.

8.8.2 RNA transcriptome research

Genome-wide transcriptome studies of ribonucleic acid (RNA) isolated from tumor biopsies are planned in this study by measuring the relative abundances of the RNA transcripts. This will enable the evaluation of changes in transcriptome profiles that may increase understanding of the pathogenesis of cancer and related conditions, the participant's response to amcenestrant, and disease subtypes, and possibly to identify new drug targets or biomarkers.

The samples may be analyzed by RNAseq or similar technologies.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable additional analysis of RNA biomarkers to increase understanding of amcenestrant and/or cancer or related diseases, and potentially to identify new drug targets or biomarkers.

8.8.3 Future use of samples

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For participants who have consented to it, the samples that are unused or left over after testing may be used for other research purposes related to oncology than those defined in the present protocol (excluding genetic analysis conducted primarily to provide information on the likelihood of developing diseases other than cancer or related conditions).

These other research analyses will help to understand either the disease or IMP response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers. These samples will remain labeled with the same identifiers used during the study. They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting participant confidentiality and personal data.

8.9 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This study is designed to test:

- The null hypothesis that the true log-fold change in Ki67 after a 14-day treatment period for both amcenestrant arms and the control arm are the same.
- The alternative hypothesis that the true log-fold change in Ki67 after 14-day treatment period is greater for either of amcenestrant arm compared to the control arm.

9.2 SAMPLE SIZE DETERMINATION

The sample size is determined based on the following assumptions:

- The geometric mean of percentage change in Ki67 after a 14-day treatment period for the control arm is assumed to be 70% (5, 16, 17).
- The geometric mean of reduction in Ki67 after a 14-day treatment period is increased to 85% for each amcenestrant arm. Therefore the geometric means of residual Ki67 (defined as one minus the geometric mean of reduction) are assumed to be 30% for the control arm and 15% for treatment arms, corresponding to a log fold difference of -0.693 (log(0.15)-log(0.3)) under the alternative hypothesis.
- The standard deviation of the log-fold change after a 14-day treatment period is assumed to be 1.

A total of 40 evaluable participants (where evaluable are defined as participants who have both baseline and post treatment available biopsies with Ki67 values) per treatment arm will be needed, in order to achieve 85% marginal power at the overall one-sided Type I error rate of 2.5% controlled with an Hochberg procedure, based on a one-sided t-test on the log-transformed data. The disjunctive power, ie, the probability to reject at least one null hypothesis associated with the comparison amcenestrant and the control arm, is estimated at 91.5%.

Allowing for a 5% non-evaluable participant rate, the total sample size for randomization is 126 participants (42 per treatment arm).

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 4):

Table 4 - Populations for analyses

Population	Description
Enrolled	All participants who sign the informed consent form
Intent-to-treat (ITT) population	All participants from the enrolled population 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 population will be used for analysis of baseline parameters.
Modified ITT (mITT) population	All participants from the ITT population who have taken at least one drug, and who have both baseline and post treatment available biopsies with Ki67 values. This is the primary analysis population for all pharmacodynamic and efficacy parameters
Per-protocol (PP) population	All participants from the mITT population without relevant deviation(s), which could affect the evaluation of the study drug on the primary endpoint. Details of relevant deviations would be further specified in the statistical analysis plan. PP population will be used for sensitivity analysis of the primary endpoint.
Safety	All participants randomly assigned to study intervention and who take 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
Pharmacokinetic-evaluable	All participants from the safety population who receive at least one dose of amcenestrant and with at least 1 evaluable post-treatment plasma concentration.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy/pharmacodynamics analyses

All efficacy and pharmacodynamics analyses will be performed on the mITT population unless stated otherwise. Analysis for the primary endpoint, and the secondary endpoint of proportion of participants with a relative decrease from baseline in Ki67 ≥50%, will be repeated on the PP population as sensitivity analysis.

Table 5 - Efficacy/pharmacodynamics analyses

Endpoint	Statistical Analysis Methods
Primary	
Change in Ki67 after a 14-day treatment period compared to baseline	Analysis of covariance (ANCOVA) model on the log transformed values for hypothesis testing using the Hochberg step-up procedure for multiplicity adjustment
Secondary	
The proportion of participants with a relative decrease from baseline in Ki67 ≥50%	Descriptive statistics by treatment arm and Clopper-Pearson method for CI calculation
Change from baseline in ER expression	Descriptive statistics by treatment arm
Tertiary/Exploratory	Will be described in the statistical analysis plan (SAP)

9.4.1.1 Analysis of primary endpoint

On the assumption of a log-normal distribution, the Ki67 values will be log-transformed before analysis. The change of log(Ki67) between baseline and after a 14-day treatment period will be compared between groups using an analysis of covariance (ANCOVA) model adjusting for baseline Ki67 expression. For each group, the geometric mean of Ki67 at baseline and after a 14-day treatment period and the geometric mean of percentage reduction in Ki67 will be provided along with the 95% confidence interval. The geometric mean ratio of proportional change of Ki67 between groups and associated 95% confidence interval will be provided.

The assumption on normality of log transformed Ki67 values will be addressed before performing the proposed ANCOVA. In case this assumption is not fulfilled, alternative non-parametric (ie, Wilcoxon Mann-Whitney) test may be used.

Due to the multiplicity of tests as each amcenestrant dose/regimen will be compared to the control arm, a Hochberg step-up procedure will be used to control the overall one-sided Type I error rate of 2.5%.

9.4.1.2 Analysis of secondary endpoints

Relative decrease from baseline in Ki67 ≥50%

The proportion of participants with a relative decrease from baseline in Ki67 ≥50% between baseline and after a 14-day treatment will be provided for each treatment arm along with the 95% CI computed using the Clopper-Pearson method.

ER degradation

Change from baseline in ER expression as measured by H-Score will be summarized for each arm.

9.4.2 Safety analyses

All safety analyses will be performed on the Safety Population.

Table 6 - Safety analyses

Endpoint	Statistical Analysis Methods
Primary	No primary endpoint is defined for safety analyses
Secondary	
AEs/SAEs and laboratory abnormalities	Descriptive statistics
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2.1 Analysis of adverse events

The observation period will be divided into 3 segments:

- The pre-treatment period is defined as the time from when the participants give informed consent to the first administration of the IMP.
- The on-treatment period is defined as the time from the first dose of IMP up to last dose of IMP.
- The post-treatment safety follow-up period is defined as the time from last administration of the IMP to the last administration of the IMP + 30 days.

Pretreatment AEs are defined as any AE occurring during the pretreatment period.
Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator's opinion), or become serious during

- on treatment period only, or
- the period including both the on-treatment and post-treatment period

All TEAE analyses will be produced for the two analysis periods as listed above. Pretreatment AEs will be described separately.

Treatment-emergent AEs 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 PT, the maximum grade will be used.

An overall summary of TEAEs will be provided. The number and percentage of participants who experience any of the following will be provided:

- Treatment-emergent AEs
- Grade ≥3 TEAEs
- Grade 5 TEAEs (any TEAE with a fatal outcome during the on-treatment period)
- Serious TEAEs

- Treatment-emergent AEs leading to definitive treatment discontinuation
- Treatment-related TEAEs
- Treatment-related TEAEs Grade ≥3
- Serious treatment-related TEAEs.

Number and percentage of participants experiencing TEAEs by primary SOC and PT will be summarized by NCI-CTCAE v5.0 grade (all grades and Grade ≥3) for the safety population. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to definitive discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period.

9.4.2.2 Analyses of clinical laboratory evaluations

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 (ie, all grades and by grade) using the worst grade during the on-treatment period will be provided for the safety population.

When the NCI-CTCAE v5.0 grading scale is not applicable, the number of participants with laboratory abnormality out-of-normal laboratory range value will be displayed.

9.4.3 Other analyses

Data from other assessments (including ECGs and vital signs) will be summarized and listed, clinically significant values will be flagged, and any other information collected will be listed as appropriate.

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. Pharmacokinetic/pharmacodynamic analyses will be described in the SAP or in a dedicated PK/PD SAP.

9.5 INTERIM ANALYSES

There are no interim analyses planned for this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 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
- The protocol, protocol amendments, ICF, Investigator Brochure, 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.
- 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
  - 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

10.1.2 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.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, 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.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory 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.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation).

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 afro American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)".

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

10.1.5 Committees structure

There are no study committees in this protocol.

10.1.6 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee 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).
- 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.
- 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.
- 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.

10.1.7 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publically 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 participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance 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 to clinicalstudydatarequest.com.

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 can be found at this web address: clinicalstudydatarequest.com.

10.1.8 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.

10.1.9 Study and site closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. 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 Sponsor, as well as reasons for the early closure of a study site by the Sponsor 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

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results.
  In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

The tests detailed in Table 7 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 7 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	Blood urea nitrogen (BUN) or urea Creatinine Glucose fasting Potassium Sodium Calcium Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase Total and direct bilirubin Total protein
Coagulation	Prothrombin time International normalized ratio (INR)
Other screening tests	Follicle-stimulating hormone (as needed to confirm postmenopausal status) Viral serologies including hepatitis A antigen or IgM hepatitis A antibody, HBs antigen or hepatitis B viral DNA, hepatitis C antibody or quantitative hepatitis C viral (HCV) ribonucleic acid (RNA) The results of each test must be entered into the CRF

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

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.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology or clinical chemistry) 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 fulfil 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.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence 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 detained (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 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 in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be

immediately life-threatening or result in death or hospitalization but 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.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. 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.
- 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 using NCI-CTCAE v5.0.

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 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 the 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 the Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a 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 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.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

REPORTING OF SAES

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool in order 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 medical monitor by telephone.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

Not applicable as this study enrolls postmenopausal women.

COLLECTION OF PREGNANCY INFORMATION:

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. 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. Follow-up will be required until outcome of pregnancy. 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 will be reported as an AE or SAE. A spontaneous abortion 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 of the protocol. 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 or be withdrawn from the study.

10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA

- 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, biopsy samples, plasma samples (for cfDNA) and blood sample (for DMET genotyping) will be collected for DNA analysis.
- DNA samples will be used for research related to amcenestrant and related diseases. They may also be used to develop tests/assays including diagnostic tests related to amcenestrant and cancer. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be analyzed for mutations in genes related to cancer and/or the response to amcenestrant. Additional analyses may be conducted if it is hypothesized that this may help with interpretation of the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to amcenestrant or study interventions of this class to understand study cancer or related conditions.
- In addition, saliva will be collected pre-treatment as a source of normal reference DNA for comparison with the tumor-derived DNA data. Sequencing may be performed on the DNA from the saliva sample.
- 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 no longer than 15 years following the last participant's last visit for the study, or other period as per local requirements.

10.6 APPENDIX 6: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.7 APPENDIX 7: ABBREVIATIONS

^{18}F-FES-PET:	fluoroestradiol positron emission tomography
ADME:	absorption distribution metabolism and excretion
AE:	adverse event
AESI:	adverse event of special interest
AI:	aromatase inhibitor
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariences
AST:	aspartate aminotransferase
BCRP:	breast cancer resistance protein
BCSS:	breast cancer specific survival
CBR:	clinical benefit rate
CCCA:	complete cell cycle arrest
cfDNA:	cell free deoxyribonucleic acid
CI:	confidence interval
CIOMS:	council for international organizations of medical sciences
CONSORT:	consolidated standards of reporting trials
CRF:	case report form
CTFG:	clinical trial facilitation group
CYP:	cytochrome P
DLT:	dose limiting toxicity
DMET:	drug metabolizing enzymes and transporters
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eGFR:	estimated glomerular filtration rate
ER:	estrogen receptor
ERα:	estrogen receptor alpha
FFPE:	formalin fixed paraffin embedded
FISH:	fluorescence in-situ hybridization
GCP:	good clinical practice
GGT:	gamma-glutamyl transferase
HER2:	human epidermal growth factor receptor 2
HRT:	hormone replacment therapy
IB:	investigator's brochure
ICF:	informed consent form
ICH:	international council for harmonization
IEC:	independent ethic committee
IHC:	immuno histochemistry
IMP:	investigational medicinal product
INR:	international normalized ratio
IRB:	institutional review board
IRT:	Interactive Response Technology
LFT:	liver function test

mBC:	metastatic breast cancer
MDRD:	modification of diet in renal disease
mITT:	modified intent-to-treat
NCI CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
pCR:	pathological complete response
PD:	pharmacodynamics
PEPI:	preoperative endocrine prognostic index
P-gp:	P-glycoprotein
PgR:	progesterone receptors
PK:	pharmacokinetic
pN:	pathological node
PO:	oral dose
PP:	per protocol
PPI:	proton pump inhibitors
PR:	partial response
pT:	pathological tumor
QD:	once daily
RFS:	relapse-free survival
RNA:	ribonucleic acid
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	stable disease
SERD:	selective estrogen receptor degrader
SoA:	schedule of activties
SUSAR:	suspected unexpected serious adverse reactions
TEAE:	treatment emergent adverse events
UGT:	uridine 5'-phospho-glucoronosyltransferase
ULN:	upper limit of normal
US:	United States
UV:	ultraviolet

10.8 APPENDIX 8: LIST OF STRONG CYP3A4 INDUCERS

Concomitant administration of medications that are strong CYP3A inducers are not permitted throughout the active treatment phase in the amcenestrant treatment arms.

The following tables were extracted in October 2020 from the Drug Interaction Database from the University of Washington (www.druginteractioninfo.org).

Table 8 - Strong CYP3A inducers

Inducers	Therapeutic Class	Victim (oral unless otherwise specified)	Max AUCR	Precipitant dose (oral)
Strong Inducers (AUCR ≤0.2 or CL Ratio ≥5)				
Rifampin	Antibiotics	Budesoinide	0.003	600 mg QD (7 days)
Mitotane	Other Antineoplastics	Midazolam	0.06	Maximum of 3.5g TID (chronic therapy)
Avasimibe	Other Antilipemics	Midazolam	0.07	750 mg/day (7 days)
Rifapentine	Antibiotics	Midazolam	0.07	20 mg/kg QD (14days)
Apalutamide	Antiandrogens	Midazolam	0.08	240 mg QD (29 days)
Ivosidenib	Cancer Treatments	Midazolam	0.10 (PBPK)	1200 mg QD (19 days; PBPK modeling)
Phenytoin	Anticonvulsants	Nisoldipine	0.11	200-450 mg/day (chronic treatment)
Carbamazepine	Anticonvulsants	Quetiapine	0.13	200 mg TID (26 days)
Enzalutamide	Antiandrogens	Midazolam	0.14	160 mg QD (85±3 days)
St John's Wort extract	Herbal Medicines	Midazolam	0.20	300 mg TID (14 days)
Lumacaftor	Cystic Fibrosis Treatments	Ivacaftor	0.20	Not provided
Phenobarbital	Anticonvulsants	Verapamil	0.23	100 mg QD (21 days)

AUC = area under the curve; CL = clearance; QD = once daily; TID = three times a day.

10.9 APPENDIX 9: LIST OF CYP SENSITIVE SUBSTRATES

In vivo, amcenestrant is a moderate CYP3A inducer, and in vitro a potential inducer of CYP2B6 and CYP2Cs family. Therefore, study participants receiving amcenestrant and treated or intended to be treated with the following drugs presented as CYP sensitive substrates should be carefully monitored since it may result in loss of efficacy of these agents.

The tables for CYP sensitive substrates were extracted in October 2020 from the Drug- Drug Interaction Database from the University of Washington (www.druginteractioninfo.org). Some known substrates of the enzymes may not be listed because they do not have changes in exposure reaching sufficient level or may not have DDI studies with AUC/CL changes available.

Table 9 - In vivo CYP3A sensitive substrate

Drug (oral)	Therapeutic Class
alfentanil	Opioids
alisporivir	Antivirals
almorexant	Hypnotics - Sedatives
alpha-dihydroergocryptine	Dopaminergic Agonists
aplaviroc	CCR5 Receptor Antagonists
aprepitant	Neurokinin-1 Receptor Antagonists
asunaprevir	Antivirals
atazanavir	Protease Inhibitors
atorvastatin	HMG CoA Reductase Inhibitors (Statins)
avanafil	Erectile Dysfunction Treatments
blonanserin	Antipsychotics
brecanavir	Protease Inhibitors
brotizolam	Benzodiazepines
budesonide	Corticosteroids
buspirone	Anxiolytics
capravirine	Antivirals
casopitant	Neurokinin-1 Receptor Antagonists
conivaptan	Vasopressin Antagonists
danoprevir	Antivirals
darifenacin	Muscarinic Antagonists
darunavir	Protease Inhibitors
dronedarone	Antiarrhythmics
ebastine	H1 Receptor Antagonists
eletriptan	Triptans
eliglustat (in subjects CYP2D6 PMs)	Glucosylceramide Synthase Inhibitors
elvitegravir	HIV-Integrase Strand Transfer Inhibitors
eplerenone	Diuretics
everolimus	Immunosuppressants
felodipine	Calcium Channel Blockers
indinavir	Protease Inhibitors
isavuconazole	Antifungals
itacitinib	Kinase Inhibitors
ivabradine	Cardiovascular Drugs

Drug (oral)	Therapeutic Class
ivacaftor	Miscellaneous Agents
levomethadyl (LAAM)	Drug Addiction Treatments
lomitapide	Other Antilipemics
lopinavir	Protease Inhibitors
lovastatin	HMG CoA Reductase Inhibitors (Statins)
lumefantrine	Antimalarials
lurasidone	Antipsychotics
maraviroc	CCR5 Receptor Antagonists
midazolam	Benzodiazepines
morphothiadin	Antivirals
naloxegol	Gastrointestinal Agents
nisoldipine	Calcium Channel Blockers
paritaprevir	Antivirals
perospirone	Antipsychotics
quetiapine	Antipsychotics
saquinavir	Protease Inhibitors
sildenafil	Erectile Dysfunction Treatments
simeprevir	Protease Inhibitors
simvastatin	HMG CoA Reductase Inhibitors (Statins)
sirolimus	Immunosuppressants
tacrolimus	Immunosuppressants
terfenadine	H1 Receptor Antagonists
ticagrelor	Anticoagulants and Antiplatelets
tilidine	Treatments of Pain and Inflammation
tipranavir	Protease Inhibitors
tolvaptan	Vasopressin Antagonists
triazolam	Benzodiazepines
ubrogepant	Migraine Treatments
ulipristal	Hormones
vardenafil	Erectile Dysfunction Treatments
vicriviroc	CCR5 Receptor Antagonists
vilaprisan	Progesterone Receptor Modulator
voclosporin	Immunosuppressants

Note: The present list includes CYP3A substrates with AUC Ratio of at least 5 when co-administrated with strong CYP3 inhibitor.

Table 10 - In vivo CYP2B6 sensitive substrate

Substrate (oral)	Therapeutic Class
bupropion	Anticoagulants and Antiplatelets
efavirenz	Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Note: There are no CYP2B6 substrates with AUC Ratio of at least 5, or decrease in oral CL of 80% or more. However, bupropion and efavirenz are considered the most sensitive substrates studied.

Table 11 - In vivo CYP2C8 sensitive substrate

Substrate (oral)	Therapeutic Class
daprodustat	Other
dasabuvir	Antivirals
repaglinide	Meglitinides

Note: The present list includes CYP2C8 substrates with AUC Ratios ≥5 or CL Ratios ≤0.20.

Table 12 - In vivo CYP2C9 sensitive substrate

Substrate (oral)	Therapeutic Class
tolbutamide	Sulfonylureas
(S)-warfarin	Anticoagulants and Antiplatelets
benzbromarone	Anticoagulants and Antiplatelets
celecoxib	NSAIDS
ibuprofen	NSAIDS
glimepiride	Sulfonylureas
glipizide	Sulfonylureas
lornoxicam	NSAIDS
meloxicam	NSAIDS
piroxicam	NSAIDS

Note: The present list includes CYP2C9 substrates with AUCR ≥5 or CL Ratio ≤0.20

Table 13 - In vivo CYP2C9 sensitive substrate

Substrate (oral)	Therapeutic Class
lansoprazole (dexlansoprazol)	Proton Pump Inhibitors
(S)-mephenytoin	Anticonvulsants
omeprazole	Proton Pump Inhibitors
tilidine	Treatments of Pain and Inflammation
(R)-(-)-hexobarbital	Hypnotics - Sedatives
(R)-mephobarbital	Anticonvulsants
clobazam (parent drug)	Benzodiazepines
diazepam	Benzodiazepines
gliclazide	Sulfonylureas
pantoprazole	Proton Pump Inhibitors
proguanil (prodrug)	Antimalarials
rabeprazole	Proton Pump Inhibitors

Note: The present list includes CYP2C19 substrates with an AUCR ≥5, or CL ratio ≤0.20.

In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and, moderately, 2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

10.10 APPENDIX 10: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Table 14 - ECOG performance status scale

Grade	Description
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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

10.11 APPENDIX 11: EASTERN COOPERATIVE ONCOLOGY GROUP RESPONSE CRITERIA

Table 15 - ECOG response criteria

Complete Response	Clinical: Complete disappearance of all clinically detectable malignant disease Pathologic: Pathologic proof of a clinically complete response after repeat biopsy of areas of known malignant disease
Partial Response	≥50% decrease in tumor area (multiplication of longest diameter by the greatest perpendicular diameter), or ≥50% decrease in the sum of products of the perpendicular diameters of multiple lesions in the same organ site, or decrease in uni-dimensional measurable disease of ≥30%, without increase in size of any area of known malignant disease of ≥25% or appearance of new areas of malignant disease
Stable Disease	No significant change in measurable or evaluable disease: • No increase in size of any known malignant disease • No appearance of new areas of malignant disease • This designation includes - Decrease in tumor area of in the sum of products of the individual lesions of <50% OR - Decrease in uni-dimensional measurable disease of <30% OR - Increase in size of any area of known malignant disease of <25% in any site • No deterioration in ECOG performance status of ≥1 level related to malignant disease
Progressive Disease	• Significant increase in size of lesions present at the start of therapy or after a response - ≥25% in the area of any malignant lesions >2 cm^2 or in the sum of products of the individual lesions, or - ≥50% in the area if only one lesion is measurable and was ≤2 cm^2 at the initiation of therapy OR • Appearance of new metastatic lesions known not to be present at the start of therapy OR • Stable objective disease associated with deterioration in ECOG performance status of ≥1 level related to malignancy

Repeat measurement should be performed at the same pre-therapy site(s) of malignant disease.
Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

10.12 APPENDIX 12: PREOPERATIVE ENDOCRINE PROGNOSTIC INDEX

Table 16 - Preoperative endocrine prognostic index (PEPI)

Pathology, biomarker status	Relapse-Free Survival (RFS)	Breast Cancer-Specific Survival (BCSS)
Pathological tumor size		
T1/2	0	0
T3/4	3	3
Node status		
Negative	0	0
Positive	3	3
Ki67		
0%-2.7% (0-1*)	0	0
>2.7%-7.3% (1-2*)	1	1
>7.3%-19.7% (2-3*)	1	2
>19.7%-53.1% (3-4*)	2	3
>53.1% (>4*)	3	3
ER status, Allred score		
0-2	3	3
3-8	0	0

* The natural logarithm interval corresponding to the percent Ki67 values on the original percentage scale
Source: Matthew J. Ellis, Yu Tao, Jingqin Luo, et al. Outcome Prediction for Estrogen Receptor – Positive Breast Cancer Based on Postneoadjuvant Endocrine Therapy Tumor Characteristics. J Natl Cancer Inst. 2008;100:1380-8.

10.13 APPENDIX 13: ABBREVIATED MODIFICATION OF DIET IN RENAL DISEASE FORMULA

GFR (mL/min/1.73 m^2) = 175 × (Scr) $^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if Female) × (1.212 if black race).

GFR = Glomerular Filtration rate, Scr = Serum creatinine in mg/dL, Age in years

Source: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/mdrd-adults-conventional-units.

GFR calculator can be found via https://www.mdcalc.com/mdrd-gfr-equation.

10.14 APPENDIX 14: 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. However, in case new participant 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.

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) (Section 8). 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, 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.

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 10.1.3).

10.15 Appendix 15: PROTOCOL AMENDMENT HISTORY

Amendment 01 dated 20-Jan-2020

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activities	Added details on information to be completed for demography and added the follicle stimulating hormone (FSH) test	For completeness and consistency
Section 1.3, schedule of activities, Section 8.7 genetics and Section 10.5 genetics	Added one blood sample for SAR439859 treatment arms to investigate allelic variants of drug metabolizing enzymes and/or drug transporters	To investigate drug metabolism enzyme variants (eg, UGT1A1 and UGT1A4) as intrinsic factors associated with PK of PK variability of SAR439859 according to FDA's comments
Section 1.3 schedule of activities, Section 7.1.1 definitive discontinuation and Section 8.6.1 tumor biopsy	Revised "biopsy from surgery specimen" to "core-cut biopsy from surgery specimen"	To clarify the requirement of surgical specimen handling
Section 1.3 schedule of activities; Section 8.6.1 tumor biopsy	"For clinical sites reporting Ki67 expression by range rather than a single value, a local re-evaluation might be requested to confirm Ki67 expression ≥15%." was added.	To clarify that the precise value of Ki67 is needed to evaluate the patient's eligibility, especially when ki67 is reported as 11-20% by the local lab.
Section 4.3 Justification for dose	Revised safety data language according to new approved version of IB (3.0)	To be in line with the new approved version of IB (3.0) of SAR439859.
Section 5.1 Inclusion criteria	Modified I03 to add Stage I patients and patients intended for upfront mastectomy	Stage I patients could be included if the minimum tumor size is ≥10 mm, and patients intended for upfront mastectomy should not be excluded in this study.
Section 5.1 Inclusion criteria and Section 10.4 Contraception guidance	Modified I04 to remove premenopausal women on GnRH analog and perimenopausal women (cessation of menses of duration ≤12 months), and modified text in Appendix 4 accordingly	It's not proper to compare post-therapy biopsy tissue versus baseline biopsy tissue in case GnRH analog is given in-between. It is also difficult to diagnose menopause for perimenopausal women by the FSH test. Hence premenopausal women on a GnRH and perimenopausal woman will not be included.
Section 5.1 Inclusion criteria	In I05, "A breast tumor size of at least 10 mm in short axis measured by ultrasound" was replaced by "A breast tumor size of at least 10 mm in greatest dimension measured by ultrasound"	According to AJCC Cancer Staging Manual 8th edition 2017, the size of tumor refers to the greatest dimension.
Section 5.2 Exclusion criteria	E08, "Currently receiving (and unwilling to discontinue) hormone replacement therapy (last dose <14 days prior to randomization)" was replaced by "Recent use of hormone replacement therapy (last dose ≤30 days prior to randomization)"	Discontinuing HRT could have impact on the tumor including analysis of key biomarkers such as Ki67. So the washout duration of HRT should be at least 30 days prior to randomization.
Section 5.2 exclusion criteria	"E16 Men" was deleted.	It's a duplicated information with I10

Section # and Name	Description of Change	Brief Rationale
Section 5.2 exclusion criteria; Section 6.5 Concomitant therapy	New exclusion criteria E21 added. And drugs that are potential inhibitors of UGTs are moved to the list of prohibited therapies/medications	To be in line with the IB of SAR439859, drugs that are potential inhibitors of UGTs are added to the exclusion criteria and the list of prohibited therapies/medications.
Section 5.3 lifestyle consideration; Section 6.5 concomitant therapy	The duration of sun protection for patients taking SAR439859 was extended from "during study treatment" to "during study treatment and for at least 5 days after discontinuation of SAR439859"	SAR439859 is expected to be eliminated from plasma after 5 times plasma half-life (approximately 24 hours). So, it is recommended that sun screen should be used during the treatment and at least 5 days after discontinuation of SAR439859.
Section 6.6 Dose modification	Dose modification criteria for SAR439859 and letrozole was modified to not allow any dose modification or reintroduction of study treatment for NCI CTCAE Grade $\geq$3 AEs.	There is no justification to re-challenge SAR439859 or letrozole to a patient after the first occurrence of Grade ≥3 AE considering the short period of treatment (ie, 14 days) while in addition no direct benefit is intended to the patient in this study.
Section 8.3 AE and SAE	"symptomatic overdose has to be reported as a standard AE." replaced to "asymptomatic overdose has to be reported as a standard AE."	Error correction
Section 8.6.1 tumor biopsy	Diagnostic biopsy baseline sample timelines changed from "within 3 months prior to randomization" To "within 4 weeks prior to randomization" "No hormone replacement treatment administrated from 30 days prior to diagnostic biopsy till screening" added.	Clarification to be closer to the clinical practice. Discontinuing HRT could have impact on the tumor cell. If HRT is used within 30 days prior to diagnostic biopsy, the diagnostic biopsy should not be adopted as baseline sample.
Section 8.6.1 tumor biopsy	The fixing time for the tumor biopsy sample is revised from 24-48 hours to 24-72 hours prior to processing and embedding at local pathology centers.	To keep consistent with the updated requirements on tumor sample fixing in lab manual.
Section 8.7 Genetics and Section 10.5 Genetics	"Genome-wide sequencing of DNA isolated from a tumor biopsy" is revised to "Mutation analysis of DNA isolated from a tumor biopsy", and "or analysis of the entire genome" is deleted	Genetic research will be proceeded with targeted panel, not Whole Exome Sequencing.
Section 10.2 Clinical laboratory tests	Estradiol is removed from screening tests	Only FSH test is needed to confirm the postmenopausal status of the patients. Estradiol is not needed in this study.
Throughout the amended protocol	Performed administrative and editorial updates and corrections.	To improve consistency and clarity.

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