NCT04191382

STATISTICAL ANALYSIS PLAN

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

SAR439859-ACT16106

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATC:	anatomical, therapeutic and chemical
BCL2:	B-Cell Lymphoma 2
BUN:	blood urea nitrogen
cfDNA:	cell-free DNA
CI:	confidence interval
CTCAE:	Common Terminology Criteria for Adverse Events
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
ER:	estrogen receptor
HER2:	human epidermal growth factor receptor 2
INR:	international normalized ratio
ITT:	intent-to-treat
MedDRA:	Medical Dictionary of Regulatory Activities
mITT:	modified ITT
MRD:	minimal residual rate
NCI:	National Cancer Institute
PEPI:	Preoperative Endocrine Prognostic Index
PgR:	progesterone receptor
PP:	per-protocol
PT:	prothrombin time
QD:	once daily
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN

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

After a screening phase of up to 14 days, 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 surgery date should be fixed before randomization. The surgery is to be performed 1 (+1) day after the last dose of study treatment.

Approximately 126 patients will be randomized such that 120 evaluable participants are reached. A total of 40 evaluable participants per treatment arm are expected.

1.2 OBJECTIVES

1.2.1 Primary objective

The primary objective is to determine whether SAR439859 given at 2 different doses improves the antiproliferative activity when compared to letrozole.

1.2.2 Secondary objectives

The secondary objectives are:

- To assess the proportion of participants with a relative decrease from baseline in Ki67 ≥50% in the three treatment arms.
- To assess ER degradation in biopsies in participants in the three treatment arms.
- To assess safety in the three treatment arms.

1.2.3 Exploratory objectives

The exploratory objectives are:

- To assess the pharmacokinetics (PK) of SAR439859 400 mg QD and 200 mg QD.
- To assess the complete cell cycle arrest (CCCA: Ki67 ≤2.7%) rate in the three treatment arms.
- To determine the expression of additional tumor protein biomarkers (eg, BCL2) and the RNA profile over time in the three treatment arms.
- To assess protein biomarkers in tumor tissues by using digital image-based methods and changes over time in the three treatment arms.

- To determine the DNA mutation profile in tumor and cell-free DNA (cfDNA) to assess a potential link with Ki67 effect
- To evaluate PK/PD relationship of SAR439859 with pharmacodynamics and/or safety.
- To assess the Eastern Cooperative Oncology Group (ECOG) clinical response rate in the three treatment arms.
- To assess the Preoperative Endocrine Prognostic Index (PEPI) risk score of the three treatment arms
- To assess in participants the pathological complete response (pCR) of SAR439859 given at 2 different doses and letrozole

1.3 DETERMINATION OF SAMPLE SIZE

The sample size is determined based on the following assumptions:

- The geometric mean of percentage reduction in Ki67 after a 14-day treatment period for the control arm is assumed to be 70% (1, 2, 3).
- The geometric mean of reduction in Ki67 after a 14-day treatment period is increased to 85% for each SAR439859 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.

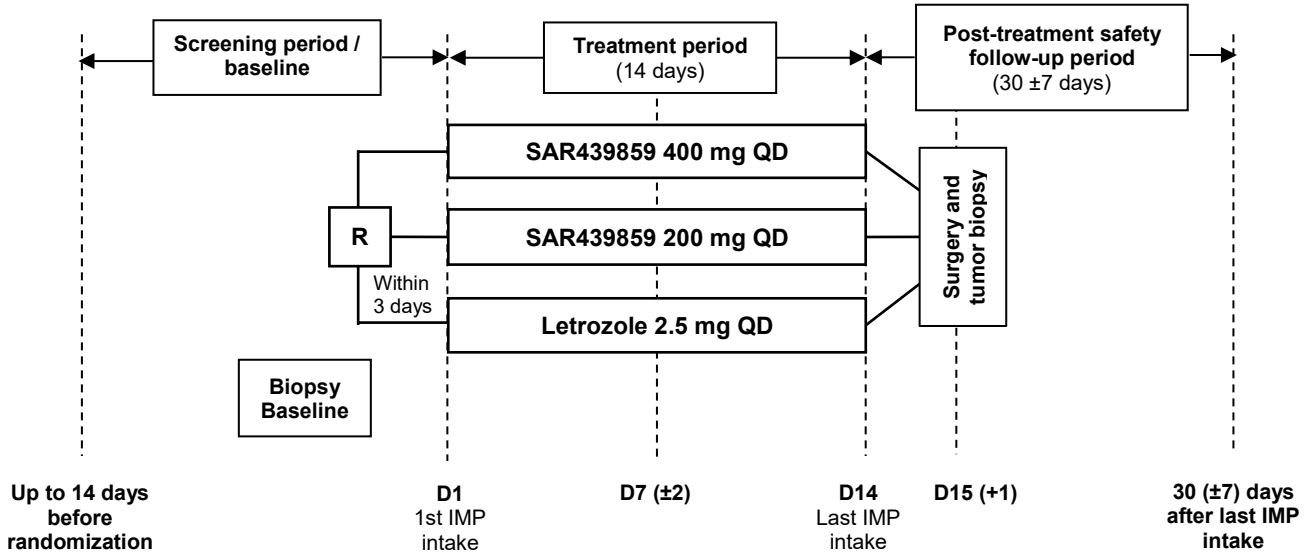
A total of 40 evaluable participants (where evaluable are defined as participants who have both baseline and post treatment available biopsies with Ki67 values) per treatment arm will be needed, in order to achieve 85% marginal power at the overall one-sided Type I error rate of 2.5% controlled with 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, that the true log-fold change in Ki67 after a 14-day treatment period for both SAR439859 arms and the control arm are the same, 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).

1.4 STUDY PLAN

Graphical study design is presented in Figure 1. Details on efficacy and safety assessments are included in Section 1.3 of the protocol.

Figure 1 - Graphical study design



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

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The protocol amendment history table below gives the timing, rational, and key details of major changes to the protocol statistical section.

Table 1 - Protocol amendment statistical changes

Amendment number	Date approved	Rationale	Description of statistical changes
2	26-Jan-2021	To add baseline Ki67 as a covariate when comparing the Ki67 log-proportional change after a 14-day treatment period between treatment groups.	Changed statistical model from t-test to analysis of covariance (ANCOVA) model.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the amended statistical analysis plan.

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
2	This version	To remove hypothesis test for primary endpoint due to early enrollment termination.	Removed p-value calculation by Hochberg procedure and multiplicity issue in Section 2.4.5.1.
2	This version	To assess the impact of Ki67 from different resource on primary analysis.	Performed primary analysis on Ki67 by each reader as sensitivity analysis in Section 2.4.5.1.3.
2	This version	To keep consistent with ICC calculation.	The derivation of the single Ki67 value used for primary analysis model has been clarified based on the average of the log transformed values instead of the average of two raw values in Section 2.1.3.1.
2	This version	To add baseline Ki67 as a covariate when comparing the log proportional change after a 14-day treatment period between treatment groups.	The statistical model has been changed from t-test to analysis of covariance (ANCOVA) model.
2	This version	To align with Protocol Amendment 02	Added Complete Cell Cycle Arrest (CCCA) as an exploratory endpoint in Section 2.1.3.3 and corresponding analyses in Section 2.4.5.4.

SAP version number	Date approved	Rationale	Description of statistical changes
2	This version	Based on the findings of the POETIC trial (4), patients with a high Ki67 at baseline (ie, ≥10%) and a low Ki67 (ie, <10%) after 2 weeks of AI had a lower 5-years recurrence rate than patients with a high Ki67 at both baseline and after 2 weeks of AI.	Added post-treatment Ki67 <10% as an exploratory endpoint in Section 2.1.3.3 and corresponding analyses in Section 2.4.5.4.
2	This version	To align with Protocol Amendment 02.	Added photosensitivity reaction in AESI in Section 2.1.4.1
2	This version	To detail the analysis of additional tumor protein biomarkers.	Specified the analysis for additional protein biomarkers (PgR, BCL2, Cyclin D1 etc) in Section 2.4.7.2.2
2	This version	Additional analyses of ECG were added to further safety evaluation.	The following analyses have been added: • Abnormalities analyses • Descriptive statistics and plots • Validation of the QT correction • Concentration-ECG analyses
2	This version	To detail the model used in primary analysis.	Added appendix of Technical details for primary analysis
2	This version	To add ECG criteria for potentially significant abnormalities as reference.	Added appendix of ECG criteria for potentially significant abnormalities - for Phase 2/3 studies (oncology only)

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last value or measurement taken up to the date and time of the first dose of study treatment irrespective of the treatment. This definition applies for all variables unless otherwise specified.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with summary statistics in the safety and efficacy sections (Section 2.4.6 and Section 2.4.5).

Demographic characteristics

Demographic variables include race (White, Black or African American, Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, Not reported, Unknown), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown), age in years (quantitative and qualitative variable: [18-64], [65-84], and ≥85 years, height, weight (kg) and ECOG performance status (PS) at baseline.

Medical or surgical history

Medical or surgical history includes relevant history of previous or associated pathologies other than the tumor.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at diagnosis

The following disease characteristics at initial diagnosis will be described:

- Time from initial diagnosis of breast cancer to first study treatment administration (in weeks),
- Histology
- Disease Location
- Laterality
- Histopathology type
- Stage of the disease. Stage I-IV for breast cancer will be derived from TNM information as collected in CRF based on the rules defined in Appendix A
- HER2 status
- ER status (local assessment as collected in CRF)
- PgR status (local assessment as collected in CRF)
- Ki67 level (%) (local assessment as collected in CRF, quantitative and qualitative variable: <15%, ≥15% to <20%, and ≥20%)

Disease characteristics at baseline (central assessment)

- Ki67 level (%) (quantitative and qualitative variable: <15%, ≥15% to <20%, and ≥20%)
- ER status
- PgR status
- BCL2 status
- Cyclin D1 status

Prior anti-cancer therapies

- Prior anti-cancer treatment or radiotherapy

Patients with prior anti-cancer treatment or radiotherapy are not allowed for study participation (unless the treatment was completed 1 year before study entry). Listings of prior anti-cancer therapies, if any, will be provided for prior anti-cancer treatment as well as radiotherapy respectively.

2.1.2 Prior or concomitant medications

All medications taken from the signed informed consent date up to the first study treatment administration and until the end of the study (ie, 30 days after the end of treatment) are to be reported in the case report form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD), using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior (<) to first study treatment administration. Prior medications can be those discontinued before first administration or those ongoing during the treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the study treatment from first administration to the last administration +30 days. A given medication can be classified both as a prior medication and as a concomitant medication.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.3.

2.1.3 Efficacy /pharmacodynamics endpoints

2.1.3.1 Primary endpoint(s)

The primary endpoint is the percentage reduction in Ki67 level after a 14-day treatment period compared to baseline. Ki67 level is expressed in terms of percentage of positive tumor cells tested by immunohistochemistry [IHC]) and will be recorded independently by 2 histopathologists. A single Ki67 result derived by the antilog transformation of the mean of the log of 2 reported values, will be used for calculation. The inter-reader variability in reporting Ki67 values will be

assessed during the trial, and a third adjudicator might be involved if the agreement between two Ki67 values does not meet the pre-specified criteria (see Section 2.4.5.1.1).

The primary endpoint is calculated as: 100 × ($Ki67_{pre}$ - $Ki67_{post}$) / $Ki67_{pre}$, where $Ki67_{pre}$ and $Ki67_{post}$ are used to denote the pre-treatment and post-treatment Ki67 values respectively. Since both SAR439459 and letrozole treatments intend to reduce Ki67 levels, a positive result is expected with this formula and denoting Ki67 value reduction.

2.1.3.2 Secondary endpoint(s)

Secondary efficacy endpoints are defined below.

- The proportion of participants with relative decrease from baseline in Ki67 ≥50% (ie, 100 ×($Ki67_{pre}$ - $Ki67_{post}$)/$Ki67_{pre}$ ≥50%) as tested by IHC after a 14-day treatment period compared to baseline.
- Change in ER expression H-Score after a 14-day treatment period. This endpoint is calculated as $H\text{-score}_{post}$ –$H\text{-score}_{pre}$, where $H\text{-score}_{post}$ and $H\text{-score}_{pre}$ are used the denote the post- and pre-treatment H-scores respectively.

2.1.3.3 Additional endpoint(s)

- ECOG response rate is defined as clinical complete response (cCR), pathological complete response (pCR) or partial response (PR), as measured by ultrasound according to ECOG response criteria (see Appendix B). The ECOG response (except pCR) will be assessed by investigator and collected in CRF.
- The proportion of participants achieving pCR after a 14-day treatment period. The pCR will be assessed by investigator and collected in CRF.
- PEPI risk score is the sum of the risk points derived from the pT stage, the pN stage, Ki67 levels and ER status of the surgical regimen. It will be calculated with the rules as defined in Appendix C. PEPI score will be calculated for both RFS and BCSS based scale.
- Complete cell cycle arrest (CCCA) is a marker of reduced cellular proliferation, is defined as a Ki67 ≤2.7% at D15 on central assessment.
- The proportion of participants with post-treatment Ki67 <10%.
- Additional protein expression assessments (eg, Ki67) by using digital image-based method.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, weight, electrocardiogram (ECG) and ECOG PS.

Observation period

The observation period starts from the time when the patient gives informed consent and is divided into 3 periods:

- 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 day

2.1.4.1 Adverse events variables

AEs (including serious adverse events [SAEs] and AEs of special interest [AESI]) will be collected from the time of signed informed consent until the end of study. In addition, All SAEs, non-serious AEs of special interest (as defined in Section 2.1.4.1), and non-serious AEs related to IMP still ongoing at time of study treatment discontinuation will be followed until resolution or stabilization.

Adverse event observation period

- Pretreatment AEs are defined as any AE occurring during the pretreatment period.
- Treatment-emergent AEs (TEAEs) are defined as AEs that develop, worsen (according to the Investigator's opinion), or become serious during
  - on treatment period (from first dose of IMP to last dose of IMP), or
  - on treatment and post-treatment period (from first dose of IMP to last dose of IMP +30 days)

  Analysis will be performed for both analysis periods (see Section 2.4.6.1)
- All AEs (including SAEs and AESI) will be graded according to National cancer institute common terminology for adverse events (NCI-CTCAE) v5.0 and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of MedDRA currently in effect at Sanofi at the time of database lock.

Adverse events of special interest

Specific analyses will be performed for the following AEs (see Section 2.4.6.1):

- Pregnancy occurring in a female participant entered in the clinical trial.
- Symptomatic overdose (serious or nonserious) with IMP
- Increase in alanine transaminase (ALT) ≥ Grade 2
- Photosensitivity reaction

2.1.4.2 Deaths

A listing of on-study deaths (if any) will be provided.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis including hematology and biochemistry. Clinical laboratory values will be converted into standard international units that will be used in all listings and tables.

For laboratory safety variables, parameters measured on the day of the first study treatment intake will be considered as part of the baseline measurements.

For laboratory safety variables, the treatment period will start at first study treatment intake +1 day.

The laboratory safety parameters will be classified as follows:

- Hematology
  - **Red blood cells, platelets, and white blood cells:** platelet count, red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell with differential: neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
  - **Coagulation:** prothrombin time (PT) and international normalized ratio (INR).
- Biochemistry
  - **Metabolism:** fasting glucose, total protein.
  - **Electrolytes:** potassium, sodium, calcium.
  - **Renal function:** creatinine, blood urea nitrogen (BUN), urea, eGFR
  - **Liver parameters:** alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total and direct bilirubin.
- Hormone:
  - **Follicle-stimulating hormone** (for women with non-childbearing potential)

2.1.4.4 Vital signs variables

Vital signs include: pulse rate, systolic and diastolic blood pressure, weight, temperature and ECOG PS (0, 1, 2, 3, 4, 5).

For vital signs, parameters measured on the day of the first study treatment intake will be considered as part of the baseline measurements.

For vital signs, the treatment period will start at first study treatment intake +1 day.

For a given parameter, a patient will be considered as evaluable if at least one measure of this parameter is available during the on-treatment period.

2.1.4.5 Electrocardiogram variable

Triplicate electrocardiogram assessments will be described as normal or abnormal by central reading at pre-dose on Day 1 and at pre-dose and 3h post-dose on Day 14.

Single 12-lead ECGs will be recorded at screening by local assessment and investigator's opinion (normal/abnormal) will be reported.

The following parameters will be assessed/derived and provided for statistical analysis:

- PR (in ms)
- QRS (in ms)
- QT (in ms)
- Mean RR (in ms)
- QTcB (in ms) = $QT.RR^{-0.50}$
- QTcF (in ms)=$QT.RR^{-0.33}$
- Heart rate (in bpm) = 60/RR with RR in seconds

In case of triplicates assessments, only the mean of the triplicate will be presented. All parameters will be analyzed as raw data and absolute change from baseline (raw value at visit X - baseline value). In addition, for the abnormalities analyses and descriptive statistics, PR and QRS will be also analyzed as percent change from baseline (100 x [raw value at visit X - baseline value]/baseline value). Semi-automatic reading from core lab of these quantitative parameters will be used for concentration-ECG analyses.

2.1.5 Pharmacokinetic variables

SAR439859 plasma concentrations will be determined at the predefined time point according to the SoA presented in Section 1.3 of the protocol.

In addition, population PK approaches might be used to calculate individual PK parameters estimates. The population PK analysis, if any, will be described in a separate report.

PK concentrations (and potentially PK parameter estimates) will be used to conduct an exploratory PK/PD relationship analysis of SAR439859 with pharmacodynamics (eg, Ki67) and/or safety (eg, triplicate ECG parameters, incidence of AEs).

2.1.6 Pharmacodynamic variables

2.1.6.1 Mutational profiling in circulating free DNA

Genomic analyses on circulating cell-free DNA (cfDNA) isolated from plasma samples will be performed in this study at baseline. The mutational status of a panel of 77 cancer driver genes (Roche AVENIO panel) will be determined by next generation sequencing (NGS) technology. Different types of genomic aberrations will be investigated such as single nucleotide variants,

indels, abnormal copy number variants or fusion genes. For both single nucleotide variants and indels, the type of mutation (missense, frameshift, inframe, …), the mutant allele frequency (%) and the mutant concentration (ie, the number of mutant molecules per mL plasma) will be provided.

In addition, saliva samples will be collected pre-treatment as a source of normal reference DNA for comparison with the cfDNA but also with the tumor-derived DNA (see Section 2.1.6.2) 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.

2.1.6.2 Tumor biopsy

Determination of tumor characteristics (HER2 status by IHC or FISH, ER by IHC, Ki67 by IHC, etc) on the diagnostic biopsy specimen based on local laboratory results serves for participant selection.

Biopsy samples collected at screening and after a 14-day treatment period will be centrally 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. For the assessment of agreement in Ki67 measurements, see Section 2.4.5.1.1. Ki67, ER, PgR, BCL-2 will also be collected by digital image-based method.

Genome-wide transcriptome sequencing of ribonucleic acid (RNA) isolated from tumor biopsies will be performed at screening and after a 14-day treatment period by measuring the relative abundances of the RNA transcripts through RNA sequencing. The ER activation score related to ER degradation will be derived from these RNAseq data. Other gene signatures (such as PAM50), immune cell abundances or pathways may be also explored from these data.

Finally, whole exome sequencing from tumor biopsies will be also performed at screening to highlight genomic aberrations directly from the tumor. A focus will be done on a predefined cancer research list containing around 1600 genes. As for mutational profiling from cfDNA, different types of genomic aberrations will be investigated such as single nucleotide variants, indels, abnormal copy number variants or fusion genes. For both single nucleotide variants and indels, the type of mutation (missense, frameshift, inframe, …) and the mutant allele frequency (%) will be provided. The saliva samples will be used to differentiate somatic from non-somatic mutations. The tumor mutational burden score and the microsatellite instability will be also obtained from these data.

2.1.7 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapies after discontinuation of IMP include further anti-cancer therapy, surgery and radiotherapy.

2.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patients who signed the study informed consent.

Randomized patient consists of all participants from the enrolled population and for whom there is a confirmation of successful allocation of a randomization number by IRT. This population is also referred as the intent-to-treat (ITT) population defined in Section 2.3.1.

For patient study status, the total number of patients for each one of the following categories will be presented in the clinical study report (CSR) using a flow-chart diagram or a summary table:

- Screened patients
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who completed treatment
- Patients who discontinued study treatment and reasons for permanent discontinuation
- Patients who completed study.
- Patients who did not complete the study period and reasons for study discontinuation
- Patient still on treatment (interim analysis only)

Number of screened patients, number of screen failure patients and reasons for screen failure will be summarized in a separated table. In addition, number and percentage of screened patients by country and sites will be presented.

For all categories of patients (except for the screened and nonrandomized category) percentages will be calculated using the number of patients in randomized population as the denominator.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, the following analysis populations will be summarized in a table by number of patients on the randomized population:

- Intent-to-treat population
- Modified ITT (mITT) population
- Per-protocol (PP) population
- Safety population
- Pharmacokinetic-evaluable population

Definition of study populations are provided in Section 2.3.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

- A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized twice,

  OR

- A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

- Kit dispensation without IRT transaction
- Erroneous kit dispensation
- Kit not available
- Randomization by error
- Patient randomized twice

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population.

The randomized population is defined in Section 2.2.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

2.3.1 Intent-to-treat (ITT) population

ITT population is defined as 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.

2.3.2 Modified ITT (mITT) population

mITT population is defined as 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 efficacy and pharmacodynamic parameters.

2.3.3 Per-protocol (PP) population

PP population is defined as all participants from the mITT population without relevant deviation(s), which could affect the evaluation of the study drug on the primary endpoint. PP population will be used for sensitivity analysis of the primary endpoint.

Major or critical deviations leading to exclusion from the per-protocol population is defined as follows:

- **Informed consent procedure:**
  - Patient does not sign study informed consent or informed consent is signed after study procedure
- **Inclusion/exclusion criteria:**
  - Patient without histological and cytological proven diagnosis of invasive breast adenocarcinoma
  - The localized breast cancer is not eligible for upfront breast conservative surgery or upfront mastectomy
  - Patient is not postmenopausal as per age and criteria defined in the protocol
  - The breast tumor size is less than 10 mm in short axis measured by ultrasound
  - Patient doesn't have a primary tumor positive in ER or non-overexpressing HER2 per protocol definition
  - Ki67 level is lower than 15% at diagnosis from immunohistochemistry of the tumor based on local laboratory results
  - Ki67 level is lower than 15% at baseline based on central laboratory results
  - Prior anti-cancer treatment was completed <1 year prior to inclusion into this trial
  - Patient is not female
  - Recent use of hormone replacement therapy (last dose ≤30 days prior to randomization)

- **Concomitant medications/therapy**
  - Protocol prohibited therapy/medication/vaccine administered
- **IMP management:**
  - Patient receives ≤10 days or ≥16 days of the IMP treatment
- **Randomization procedure:**
  - IMP dispensed without Randomization
  - IMP actually dispensed to the subject is different from the IMP allocated

2.3.4 Safety population

Safety population is defined as 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 at Day 1.

Randomized patients from whom it is unclear whether they took the IMP will be included in the safety population, and included in the treatment arms as randomized.

Non-randomized but treated patients will not be part of the safety population; however, their safety data will be presented separately.

This population is the primary population for the analysis of all safety parameters.

2.3.5 Pharmacokinetic population

Pharmacokinetic-evaluable population is defined as all participants from the safety population who receive at least one dose of SAR439859 and with at least 1 available post-treatment plasma concentration with adequate documentation of dosing and sampling dates and times.

2.3.6 Pharmacokinetic/pharmacodynamic population

PK/PD population is defined as all treated subjects as long as they had at least one pharmacodynamic assessment time-matched with pharmacokinetic parameters of interest. The specific population will be defined for each PK/PD analysis.

2.4 STATISTICAL METHODS

Continuous data will be summarized using the number of available data, mean, standard deviation, median, minimum and maximum for each treatment group.

Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Due to early termination of enrollment, the planned sample size will not be achieved, therefore no hypothesis test will be performed on primary endpoint, confidence intervals will be estimated as two-sided and will used for descriptive purposes only.

In summary tables, treatment arms will be presented as follows:

- SAR439859 400 mg QD (SAR439859 400 mg)
- SAR439859 200 mg QD (SAR439859 200 mg)
- Letrozole 2.5 mg QD (Letrozole 2.5 mg)

Parameters on demographics and baseline characteristics would be provided by treatment arms and overall.

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized on the ITT population using descriptive statistics. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population for any treatment group.

The medical and surgical history will be summarized according to the SOC and PT (SOC will be sorted according to the internationally agreed order (see Appendix G) and PT by overall decreasing frequency).

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the ITT population. The anti-cancer therapy will be listed separately.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and the patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, the patients may be counted several times for the same medication.

The tables for prior and concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in SAR439859 400 mg QD column. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

2.4.3 Anticancer therapies

A listing of prior anti-cancer treatment, including intent, reason of discontinuation, relapse/progression date, best response, regimen/line number, drug name, start and end date/ongoing, will be provided by patient.

A similar listing will be provided for prior radiation therapy, including location, total dose, intent, start and end date/ongoing.

2.4.4 Extent of investigational medicinal product exposure and compliance

The extent of investigational medicinal product (IMP) exposure will be assessed and summarized on the safety population (Section 2.3.4), by treatment group.

Following information will be summarized:

- Duration of exposure (days) defined as (date of last dose – date of first dose +1).
- Cumulative dose (mg): the cumulative dose is the sum of all doses during the study treatment exposure.
- Actual dose intensity (mg/day):

$$\text{ADI} = \frac{\text{Cumulative Dose (mg)}}{\text{Duration of exposure in days}}$$

- Planned dose intensity (mg/day) is the planned dose at Day 1 per protocol:
  - 400 mg/day for the SAR439859 400 mg QD group
  - 200 mg/day for the SAR439859 200 mg QD group
  - 2.5 mg/day for the letrozole 2.5 mg QD group.
- The relative dose intensity (RDI, in %) for SAR439859 or letrozole is defined as:

$$\text{Relative Dose Intensity} = \frac{\text{Actual Dose Intensity}}{\text{Planned Dose Intensity}} \times 100$$

Summary statistics will be provided for cumulative dose, actual dose intensity and relative dose intensity (according to the following categories: 0-80%, 80-100%, >100%).

Dose modifications

- Dose reduction: a dose is deemed to have been reduced if the dose taken by a patient is lower than the dose taken on the previous day or the day before dose(s) omitted.
- Dose omission: one omission corresponds to a dose with a dose equal to 0 mg/day between two non-zero doses. Several consecutive dose omissions will be counted as one episode of omission.

Dose information variables will be summarized descriptively (n, mean, standard deviation, median, minimum and maximum). Analyses will be performed based on the number of patients. The number of patients with at least one SAR439859 or letrozole dose modification with the following details will be provided:

- Number (%) of patients with at least one dose modification (reduction or omission)
- Number (%) of patients with at least one dose reduction

- Number (%) of patients with at least one dose omission
- Number (%) of dose reductions by patient according to the following categories: 0, 1, >1
- Number (%) of dose omissions by patient according to the following categories: 0, 1, >1
- Number (%) of patients with at least 4 consecutive days of dose omission

2.4.5 Analyses of efficacy/pharmacodynamics endpoints

2.4.5.1 Analysis of primary endpoint(s)

2.4.5.1.1 Primary analysis

The primary analysis will be performed on the mITT population defined in Section 2.3.2.

Ki67 at baseline ($Ki67_{pre}$), after a 14-day treatment period ($Ki67_{post}$) and the percentage reduction in Ki67 from baseline defined as $100 \times (Ki67_{pre} - Ki67_{post}) / Ki67_{pre}$ will be summarized by treatment groups using descriptive statistics (such as the number of observations, arithmetic mean, geometric mean, median, standard deviation (SD), minimum, and maximum).The geometric mean of percentage reduction in Ki67 will be calculated with 1 minus geometric mean of proportional change, where proportional change is $Ki67_{post/} Ki67_{pre}$.

The percentage reduction in Ki67 from baseline for each patient will be displayed in a waterfall plot. In the waterfall plot, patients with Ki67 level decreased after 14-day treatment will have negative percentage change. The patients will be ordered from highest positive change to smallest negative change.

Assuming Ki67 value follows a log-normal distribution, log ($Ki67_{post}$) and log ($Ki67_{pre}$) will be used to denote the logs of the post-treatment and baseline values respectively. 0.1% will be added to untransformed Ki67 with 0 value to avoid the mathematical anomaly that arises because the log of zero is minus infinity. As a consequence of the assumption of a lognormal distribution, the log proportional changes ie, $\log(Ki67_{post}/Ki67_{pre})$ is also normally distributed. The log proportional change will be compared between treatment arms using an analysis of covariance (ANCOVA) model adjusting for the log Ki67 at baseline. Geometric LS-means ratio of proportional change (and associated 95% CI) between treatment arms will be calculated from the estimate (and associated 95% CI) of the difference of least squared (LS)-means of the log-proportional change (and associated 95% CI) from the ANCOVA model and converted by antilog transformations. For each treatment arm, geometric LS-means of the proportional change from baseline (and associated 95% CI) will be obtained from the ANCOVA model after conversion by antilog transformations. Geometric LS-means of percentage reduction in Ki67 (and associated 95% confidence intervals) will be calculated with 1 minus geometric LS-means of proportional change (and associated 95% confidence intervals). Hypothesis test will not be performed due to early enrollment termination.

Details of primary analysis can be found in Appendix D.

Evaluation of inter-reader variability

The reproducibility of Ki67 measurements among readers will be estimated by calculating an intraclass correlation coefficient (ICC). The definition along with the statistical model for ICC estimation are provided in Table 3.

Table 3 - Estimation of ICC during the trial

Notation	Definition	Model	Consistency or absolute agreement
ICC	The inter-reader agreement on log proportional change from baseline in Ki67 measurement after 14-day treatment period.	Mixed-effect model adjusted for baseline covariate, based on single rating	Absolute agreement

Mean estimations along with 95% confidence intervals will be reported for the ICC. Details of ICC estimation can be found in Appendix E.

The ICC estimate will be checked at the following time-points:

- The interim analysis when 20 patients in each arm evaluable for the primary endpoint (Section 3)
- The analysis when at least 75% patients of the study completed treatment and Ki67 value available for analysis.
- The analysis when all of the patients completed treatment and Ki67 value available for analysis.

The ICC has a range of 0-1, with 1 denoting highest agreement. The ICC estimate at each analysis will be reviewed with study team, and in case a high inter-reader variability is suspected (eg, ICC <0.8), team would evaluate the necessity of inviting a third adjudicator to provide a single Ki67 result based on the readings of two assessors.

In any case, the decision as to whether adjudication will take place needs to be finalized before database lock.

2.4.5.1.2 Subgroup analyses

Evaluation of consistency

The consistency of the results from the primary analysis will be evaluated across pre-defined subgroups in patients available in the subgroup of consideration. The subgroups included but not limited are defined in Table 4. Depending upon the study results, additional subgroups may be examined, and subgroups with small sample sizes may be pooled to create a larger meaningful subgroup. For each subgroup, geometric LS-mean of percentage reduction in Ki67 with their associated 95% CIs and geometric LS-mean ratio of proportional change between treatment arms with their associated 95% CIs will be provided for each treatment arm.

Evaluation of interactions

For each pre-defined factor defined in Table 4, log-fold change in Ki67 will be analyzed using linear regression model with terms for the factor, treatment and their interaction, adjusted by log baseline Ki67. The p-value of the test of interaction will be provided.

Other prognostic factors

Since the results from the primary analysis could be impacted by confounding factors, any potential issues will be examined and, if confirmed, exploratory analysis of the primary endpoint will be done accordingly. A multiple linear regression model will be used to identify prognostic factors among the demographic and baseline characteristics factors described in the Table 4 using a stepwise selection procedure with a 15% significance level for removing effects. For significant prognostic factors identified in the multivariate model, the balance between treatment groups will be assessed.

Table 4 - Subgroup analyses

Prognostic factor	Description
Age	<65 years or ≥65 years
Race	Asian or White or Other
Tumor stage	1 or 2 or ≥ 3
Tumor size (greatest dimension)	≥10 mm to < 20mm, ≥ 20mm
Ki67 level at baseline (per central assessment)	<20% or ≥20%
ER H-score at baseline	Low ER+. (H-score 1-100) or moderate ER+ (H-score 101-200) or high ER+ (H-score 201-300).
Progesterone receptor	< 20% vs ≥20%

2.4.5.1.3 Sensitivity analyses

The primary analysis will also be performed according to each reader, respectively.

The primary analysis will be repeated in the PP population.

2.4.5.2 Analyses of secondary endpoints

Analysis of secondary endpoints will be performed primarily on the mITT population and may be performed on the PP population.

Relative* decrease *from baseline in Ki67 ≥50%

The proportion of participants with a relative decrease from baseline in Ki67 ≥50% (ie ($Ki67_{pre}$ - $Ki67_{post}$)/$Ki67_{pre}$ ≥50%) will be provided for each treatment arm along with the 95% CI computed using the Clopper-Pearson method.

Logistic regression will be used with a 50% decrease in Ki67 as the response variable to determine potential factors (as defined in Table 4) that are predictive and/or prognostic for the disease. A multivariable logistic regression model will be conducted using a stepwise selection procedure with a 15% significance level for removing effects.

ER degradation by protein expression

ER expression in H-score before and after treatment, the absolute change from baseline (defined as ER H-score$_{post}$ – ER H-score$_{pre}$) as well as the relative change from baseline (defined as 100 × (absolute change from baseline / ER H-score$_{pre}$)) will be summarized for each arm. In case differences on baseline ER H-score are observed, additional ANCOVA model on the absolute change from baseline adjusted for baseline may be performed. In that case, LS-means of the absolute change from baseline and associated 95% CI will be provided.

2.4.5.3 Additional analyses

Clinical response rate

ECOG response rate on each arm will be estimated by dividing the number of participants with clinical response (defined as clinical complete response (cCR), pathological complete response (pCR) or partial response (PR) as measured by ultrasound according to ECOG response criteria) by the number of participants from analysis population of the respective treatment arm. In addition, 95% two-sided CIs will be computed using the Clopper-Pearson method.

pCR rate

Pathological complete response rate on each randomized arm will be estimated by dividing the number of participants with complete pathological response (ie, no histologic evidence of invasive tumor cells in the surgical breast specimen and axillary nodes identified after neoadjuvant treatment) by the number of participants from the analysis population of the respective treatment arm. In addition, 95% two-sided CIs will be computed using the Clopper-Pearson method.

PEPI risk score

The total PEPI score, as defined in Section 2.1.3.3, is the sum of the risk points derived from the pT stage, the pN stage, Ki67 levels and ER status of the surgical regimen. The total score after treatment will be summarized (quantitatively and by 3 risk categories: 0 (low risk), 1-3 (medium risk) and >=4 (high risk)) for each treatment arm.

Complete cell cycle arrest (CCCA)

The proportion of participants with CCCA will be provided for each treatment arm along with the 95% CI computed using the Clopper-Pearson method.

Post-treatment Ki67 <10%

The proportion of participants with post-treatment Ki67 <10% will be provided for each treatment arm along with the 95% CI computed using the Clopper-Pearson method.

Ki67 by digital image-based method

The primary analysis defined in Section 2.4.5.1.1 (except for ICC) will be performed on Ki67 results by digital image-based method.

2.4.6 Analyses of safety data

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the safety population as defined in Section 2.3.4. Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately.

2.4.6.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Treatment emergent AEs are defined as AEs that develop, worsen (according to the Investigator's opinion), or become serious during the

- on treatment period (from first dose of IMP to last dose of IMP), or
- on treatment and post-treatment period (from first dose of IMP to last dose of IMP+30 days)

TEAE analyses will be produced for both analysis periods and therefore two sets of TEAEs tables will be generated. Pre-treatment adverse events will be described separately.

The severity grade will be taken into account in the summary. For patients with multiple occurrences of the same adverse event, the maximum (worst) grade by period of observation is used. Summaries will be provided for all grades and for grade ≥3 (including Grade 5). Missing grades, if any, will be included in the "all grades" category.

Sorting within tables ensures the same presentation for the set of all adverse events for each observation period (pre-treatment and treatment-emergent). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on the incidence of AEs of the SAR439859 400 mg QD arm.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any

  - Treatment emergent AEs
  - Grade ≥3 TEAEs
  - Grade 5 TEAE (any TEAE with a fatal outcome during the on-treatment period)
  - Serious TEAEs
  - Treatment emergent AEs leading to definitive treatment discontinuation
  - Treatment-related TEAE
  - Treatment-related TEAEs of grade ≥3
  - Serious treatment-related TEAEs
- All TEAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE.
- Most frequent (5% of patients overall, on PT) TEAE by primary SOC and PT,
- All treatment-related TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 related TEAE.

Analysis of all treatment emergent serious adverse event(s)

- All serious TEAEs by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious TEAEs, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All serious TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 serious TEAE.
- All serious treatment-related TEAEs, by primary SOC and PT, showing the number (%) of patients with at least 1 serious related TEAE.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAE leading to definitive treatment discontinuation by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE leading to treatment discontinuation.

A listing of patients with a TEAE leading to treatment discontinuation will be provided. This listing will include the TEAE, toxicity grade, relationship to study treatment and the day of occurrence.

Analysis of all treatment-emergent adverse event(s) leading to dose reduction

- All TEAEs leading to dose reduction by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE leading to dose reduction.

Analysis of adverse events of special interest

- A listing of patients with at least one AESI cited in Section 2.1.4.1 will be provided. This listing will include the category of AESI, the seriousness, the day of occurrence and the outcome.

Analysis of pre-treatment adverse events

- All pre-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.

2.4.6.2 Deaths

A listing of all deaths during the study will be provided, including the period of occurrence (eg, pretreatment, on-treatment or post-treatment follow up) and the reason of death. A table summary for number (%) of patients who died by study period and reason of death might be generated as needed.

2.4.6.3 Analyses of laboratory variables

Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters defined in Section 2.1.4.3. Each test result will be graded by NCI-CTCAE version 5.0 whenever applicable.

For hematological parameters and for some selected biochemistry parameters, Sanofi sponsor generic ranges (LLN, ULN) are defined and will be used for grading (see list of parameters in Appendix F). For other biochemistry parameters (eg, for hepatic enzymes ALT, AST, Alkaline phosphatase, total bilirubin), grading will be derived using local laboratory normal ranges. The number of patients with abnormal laboratory tests at baseline will be presented by grade and all grades together. The frequency of patients in each grade and all grades of laboratory abnormalities during treatment will be summarized. For patients with multiple occurrences of the same laboratory variable during the treatment, the maximum grade (worst) per patient will be used. The denominator used for percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period. When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade 3-4 abnormal laboratory tests.

In addition, for hematology and biochemistry toxicities, shift tables showing the number of patients in each grade at baseline by grade during the on-treatment period will be provided.

For laboratory tests for which NCI-CTCAE V5.0 scale is not applicable, potentially clinically significant abnormalities (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review (Appendix H).

PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including

nonscheduled or repeated evaluations. The incidence of PCSA any time during the on-treatment period will be summarized by treatment group irrespective of the baseline level.

Laboratory parameters for which both CTCAE grading or PCSA criteria are not applicable will be classified into low/normal/high group by means of laboratory normal ranges. For such parameters, a summary table which present the frequency of patients with any abnormal test will be provided.

2.4.6.4 Analyses of vital sign variables

Vital signs parameters are described in Section 2.1.4.4.

- Summaries of baseline, Day 7 and Day 14 (or end of treatment) assessments will be provided for all parameters (except for weight which will be assessed at baseline and D14 only).
- For ECOG performance status, a shift table will be provided for post-treatment evaluation relative to baseline.

For vital sign variables, potentially clinically significant abnormalities (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review. PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage. The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population

The incidence of PCSAs during the on-treatment period will be summarized by treatment group irrespective of the baseline and/or according to the following baseline categories:

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

2.4.6.5 Analyses of electrocardiogram variables

Abnormalities analyses

For all parameters, an “on-treatment” analysis will be performed on the safety population, using all assessments during the TEAE period including any unplanned/rechecked values.

The same definition of PCSAs (Appendix I) will be used for all parameters, whatever the source. For the PCSAs on change from baseline in corrected QT data, in case a subject experienced multiple abnormalities, she will be counted only once in the most severe category.

Counts of subjects with PCSAs will be provided in summary tables regardless of the normal or abnormal status of the baseline. This table will be presented by treatment group.

Descriptive statistics and plots

For each of the ECG parameters, descriptive statistics on baseline and changes from baseline at each post-baseline time point will be provided by treatment group. Summary plots (mean +/- SEM) will be provided by visit and treatment group.

Validation of the QT correction

In order to explore whether the QTcF interval seem to be independent from the RR intervals, the plots of the QTcF intervals versus RR (using all replicates) will be provided, separately for off-drug and on-drug data, using ECGs send by core lab. The scatter plots, the regression line, and estimator of slope with 90% confidence interval (CI) will be provided, separately for off drug and on drug and in each treatment group.

2.4.7 Analyses of pharmacokinetic and pharmacodynamic variables

2.4.7.1 Analysis of Pharmacokinetic variables

Plasma concentrations will be summarized for each SAR439859 treatment arm by time point using descriptive statistics (such as the number of observations, arithmetic and geometric mean, median, standard deviation (SD), standard error (SE), coefficient of variation (CV)%, minimum, and maximum).

Plasma concentrations will be included in the descriptive statistics if actual sampling occurs in the following predefined time windows: within 2 hours before administration for predose sample on Day 7, Day 14, [2-4h] for samples at 3h post dose on Day 14 and Day 15;

In addition, a listing of individual concentration data by time and day will be provided.

Concentrations reported as below the limit of quantification (BLQ) will be replaced by 0 for descriptive statistics.

In case PK parameters estimates are calculated and used as part of the PK/PD exploratory analysis, they will be summarized by SAR439859 treatment arm using descriptive statistics (such as the number of observations, arithmetic and geometric mean, median, standard deviation (SD), standard error (SE), coefficient of variation (CV)%, minimum, and maximum).

2.4.7.2 Pharmacodynamic variables

2.4.7.2.1 Mutational profiling in circulating free DNA

Descriptive statistics of the type of genomic aberrations at baseline will be provided. The prevalence of patients with mutations for each gene and the overall genomic profile of patients (annotated with the treatment arm and possibly other patients' characteristics) will be described. For some key genes of interest, additional analyses may be performed by treatment arm to better understand the circulating mutational profile of patients. To this end, the description of each aberration or the distribution of the mutant allele frequency, mutant concentration and abnormal

copy number variant will be also described through descriptive statistics. Some associations with baseline or pharmacodynamic variables (eg, the baseline or % change from baseline of Ki67, the change in ER expression H-Score) will be presented through descriptive statistics and graphical presentation.

The genomic aberrations detected in the cfDNA will be compared to the ones identified from the tumor biopsies.

2.4.7.2.2 Tumor biopsy analyses

The additional protein biomarkers (PgR, BCL-2, Cyclin D1 and potentially other proteins) will be analyzed similarly to the ER protein (see Section 2.4.5.2).

For tumor-related RNA data, the measurements at baseline and after a 14-day treatment in addition to the change from baseline will be described per treatment arm for each gene signature (eg, ER activation score) or immune scores by descriptive statistics and graphical visualization.

For tumor-related DNA data, the prevalence of patients with mutations for each gene and the overall genomic profile of patients (annotated with the treatment arm and possibly other patients' characteristics) will be described at baseline. For some key genes of interest, additional analyses may be performed by treatment arm to better understand the tumor mutational profile of patients. To this end, the description of each aberrattion at baseline or the evolution of the mutant allele frequency/copy number variation over time will be also described through descriptive statistics and graphical visualization. Some associations with baseline or pharmacodynamic variables (eg, the baseline or % change from baseline of Ki67, the change in ER expression H-Score) will be presented through descriptive statistics and graphical presentation. The tumor mutational burden score and the microsatellite instability will be also described with descriptive statistics per treatment arm.

2.4.8 Further therapy after discontinuation of investigational medicinal product administration during the study

A summary table will be provided for further anti-cancer therapies based on WHO-DD coding. Similar analysis will be performed for further radiotherapy.

A listing of surgery information, including the date and type of surgery, and the reason of surgery not performed (if any) will be provided.

2.4.9 Pharmacokinetic/Pharmacodynamic analysis

2.4.9.1 PK / PD analyses

Graphical presentation of SAR439859 PK concentrations (and possibly PK parameters of interest) will be done in regards of efficacy/PD endpoints. Efficacy/PD endpoint would include but may not be limited to Ki67 expressed as % change from baseline, change in ER expression H-Score or ER activation score (degradation). Plasma concentrations below LLOQ will be replaced by LLOQ/2.

2.4.9.2 Concentration-ECG analyses

Exploratory plots

The relationship between change from baseline of ECG parameters and SAR439859 concentrations will be first explored graphically, in order to investigate any potential delayed or sustained effects and the type of modeling to be done, using the following plots, by treatment group:

- Plot of mean (± SEM) change from baseline in ECG data and mean SAR439859 concentration versus time (hours post-dose) overlaid onto the same plot.
- A scatterplot for PK plasma concentration versus change from baseline in ECG parameter, including trend lines (simple linear regression and loess line)

Concentration - ECG analyses will be performed for the QTcF, heart rate, PR and QRS intervals.

Time-matched pharmacokinetic concentrations will be used.

Modeling

In case of direct and linear relationship between concentrations and change from baseline in ECG parameters (QTcF, HR, PR, and QRS), a linear mixed effect model will be carried out, with population intercept, fixed terms for nominal time, with the concentration (slope) and the baseline ECG parameter (centered baseline values: subject's baseline minus the mean of the overall population) as covariates, and with random terms for individual subject deviation from the population intercept and slope, using SAS Proc Mixed. The analysis model was the following:

$$\text{Change from Baseline in ECG parameter}_{ij} = (\alpha + Ai) + \gamma \times \text{Baseline ECG}_i + C \times \text{Time}_j + \beta \times \text{Concentration}_{ij} + e_{ij}$$

with:

- α and β are the fixed population intercept and concentration slope.
- γ is the fixed effect for the baseline ECG slope
- A_i is the random intercept for the i^{th} subject, with A_i assumed to be normally distributed with null mean and an unstructured variance-covariance matrix per subject block.
- C is the fixed effect associated with Time_j (0 for pre-dose of D14 and 1 for 3h post-dose of D14)
- e_{ij} represents i.i.d. standard normal errors.

The estimates of each effect of the model, along with their 95% confidence interval, will be provided. In addition, prediction of change from baseline in ECG parameters at selected concentrations (geometric mean concentration at 3h of D14 for each dose) will be also calculated from the model (estimates and 90% confidence intervals). The scatter plot of individual ECG values versus PK concentrations with the regression line overlaid will be also provided.

Goodness-of-fit and residual plots will be provided. In case of lack of fit (ie, the linear model is not adequate), alternative models will be explored, like linear models using transformed concentration values (eg, logarithmic concentrations) or nonlinear models (E_{max} or sigmoid E_{max} models).

The following goodness-of-fit plots were provided:

- Model observed versus predicted change from baseline in ECG (delta ECG)
- Quantile-Quantile plots of residuals
- Distribution of residuals
- Residual plots for concentration, centered baseline ECG and time
- Quantiles of concentration and change from baseline ECG overlaid with slope of the final model

Effect of SAR439859 on heart rate will be evaluated by plotting the time course of the mean change from baseline in heart rate by dose.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

Not applicable. Renal function parameter including eGFR will be collected directly via CRF.

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.3 Missing data

The analyses and summaries of continuous and categorical variables will be based on observed data only. Percentages will be calculated using as denominator the number of patients with non-missing observation in the considered population. When relevant, the number of patients with missing data is presented.

Handling of disease characteristics missing/partial dates

- If the day is missing, it will be imputed by 1.
- If the month is missing, it will be imputed by 1 (only for medical history variables).
- If the year is missing, no imputation will be performed.

Incomplete date of cancer diagnosis:

- If the day of the cancer diagnosis is missing, the date will be imputed to the first day of the month.
- If day and month of the cancer diagnosis are missing, no imputation will be done.

Handling of medication missing/partial dates

No imputation of medication (other than anti-cancer therapies) start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior and concomitant medication.

Imputation of incomplete date for post anti-cancer treatment start date

For post anti-cancer treatments, if the medication start date is missing, it will be imputed as follows:

- If the medication start day and month are missing and the medication start year is the same as treatment end year, the medication start date will be set equal to treatment end date +1.
- If the medication start day and month are missing and the medication start year is after the treatment end year, the medication start day and month will each be set to 01.
- If the medication start day is missing and medication start year and month is the same as the treatment end year and month, the medication start date will be set to the treatment end date +1.
- If the medication start day is missing and medication start month is before the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is after the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is not missing and the medication start year is after the treatment end year, the medication start day will be set to 01.
- If the medication start day, start month and start year is missing, the medication start date will be set equal to the treatment end date +1.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

- For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

- When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

Missing grade

If the grade is missing for one of the treatment emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, no imputation will be done and missing grades will be summarized in the "all grades" category.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to the regimen is missing, then the relationship to the regimen has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 GIGA/L or > ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.4 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline and worst values and/or grades.

2.5.5 Pooling of centers for statistical analyses

Data from all sites will be pooled together for analyses.

2.5.6 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

In order to support project strategic planning, an interim analysis may be conducted after the first 20 patients in each arm evaluable for the primary endpoint. The analysis will have no impact on the trial itself.

4 DATABASE LOCK

The final database lock is planned 4 weeks after last patient last visit in the study.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A TNM anatomic stage groups

When T is	And N is	And M is	Then the stage group is
Tis	N0	M0	0
T1	N0	M0	1A
T0	N1mi	M0	1B
11	N1mi	M0	1B
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

Source: Giuliano AE, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J. Clin. 2017;67:290–303. doi: 10.3322/caac.21393

Note to programmer:

T0 corresponds to “No evidence of primary tumor” as collected in CRF

N0 corresponds to “No regional lymph nodes metastasis” as collected in CRF.

M0 corresponds to “No distant metastasis” as collected in CRF.

If any of the following is checked, then the stage would be “Not evaluable”.

- Primary tumor cannot be evaluated
- No regional lymph node metastasis
- No distant metastasis.

Appendix B Eastern Cooperative Oncology Group 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, 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 in the sum of products of the individual lesions of <50% OR - Decrease in uni-dimensional measurable disease of <30% OR - Increase in 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

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

Appendix C 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, H-score 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.

Appendix D Technical Details for Primary Analysis

For each treatment arm:

- the geometric mean of Ki67 proportional change (and associated 95% CI) will be computed as

  exp (arithmetic mean of Ki67 log-proportional change)

- the geometric mean of Ki67 percent reduction (and associated 95% CI) will be computed as

  1 - geometric mean of proportional change (and associated 95% CI)

An analysis of covariance (ANCOVA) will be used to compare the Ki67 log-proportional changes between groups,

$$Y = a + bX + cZ$$

Where

- Y is log-proportional change from baseline to D14,
- X is the treatment group variable,
- Z is the log baseline Ki67, ie, $\log(Ki67_{pre})$,

Geometric LS-means ratio of proportional change (and associated 95% CI) between treatment arm will be calculated from the estimate (and associated 95% CI) of the difference of LS-means of the log-proportional change (and associated 95% CI) and converted by antilog transformations.

Appendix E Technical Details for ICC calculation

A mixed effect model will be fitted to the log proportional change of Ki67 measurement after 14-day treatment period:

$$y_{ij} = \mu + r_i + \delta X_{ij} + \varepsilon_{ij}$$

Where

- y_{ij} is the log proportional change from baseline to Day 14 in Ki67 measurement for the ith patient scored by the jth reader
- r_i is the random effect of the ith patient
- X_{ij} is the log baseline Ki67 value for the ith patient scored by the jth reader
- ε_{ij} is the residual error term

The random effects r_i, and ε_{ij} are assumed to be normally distributed with means of zero and variances of σ_1 and σ_2, respectively, and to be independent of each other.

ICC is defined by $\sigma_1 / (\sigma_1 + \sigma_2)$

Appendix F Generic ranges for hematological and biochemistry parameters

The current list of generic ranges for hematological parameters (for adults) is provided in the table below:

Table 5 - Generic ranges for hematological parameters

LBTEST	GENDOR	LBSTRESU	LBGNNRLO - LBGNNRHI
Hemoglobin	M	g/L	135 - 175
Hemoglobin	F	g/L	120 - 160
Lymphocyte		10^9/L	1 - 2
Neutrophils		10^9/L	1.8 - 3.15
Platelets		10^9/L	150 - 350
Leukocytes		10^9/L	4.5 - 11
Eosinophils		10^9/L	0 - 0.4
Basophils		10^9/L	0 - 0.15
Monocytes		10^9/L	0.18 - 0.5
Hematocrit	M	v/v	0.41 - 0.53
Hematocrit	F	v/v	0.36 - 0.46
Erythrocytes	M	10^12/L	4.5 - 5.9
Erythrocytes	F	10^12/L	4 - 5.2
INR		v/v	0.8 - 1.2

The current list of generic ranges for biochemistry parameters (for adults) is provided in the table below:

Table 6 - Generic ranges for biochemistry parameters

LBTEST	LBSTRESU	LBGNNRLO - LBGNNRHI
Albumin	g/L	35 - 55
Blood Urea Nitrogen (BUN)	mmol/L	3.6 - 7.1
Calcium	mmol/L	2.2 - 2.6
Chloride	mmol/L	80 - 115
Glucose	mmol/L	3.900001 - 6.999999
Bicarbonate (HC03)	mmol/L	22 - 29
Potassium	mmol/L	3.5 - 5
Magnesium	mmol/L	0.8 - 1.2
Sodium	mmol/L	136 - 145
Phosphate	mmol/L	1 - 1.4
Protein	g/L	55 - 80
Urea	mmol/L	3.6 - 7.1

Based on NEJM (N Engl J Med 2004;351:1548-63.): “Laboratory Reference Values”, Alexander Kratz, M.D., Ph.D., M.P.H., Maryjane Ferraro, Ph.D., M.P.H., Patrick M. Sluss, Ph.D., and Kent B. Lewandrowski, M.D.

Appendix G Internationally agreed SOC order

The internationally agreed order (Guideline on summary of product characteristics, December 1999, European commission) for SOC:

1. Infections and infestations
2. Neoplasms benign and malignant (including cysts and polyps)
3. Blood and the lymphatic system disorders
4. Immune system disorders
5. Endocrine disorders
6. Metabolism and nutrition disorders
7. Psychiatric disorders
8. Nervous system disorders
9. Eye disorders
10. Ear and labyrinth disorders
11. Cardiac disorders
12. Vascular disorders
13. Respiratory, thoracic and mediastinal disorders
14. Gastrointestinal disorders
15. Hepato-biliary disorders
16. Skin and subcutaneous tissue disorders
17. Musculoskeletal, connective tissue and bone disorders
18. Renal and urinary disorders
19. Pregnancy, puerperium and perinatal conditions
20. Reproductive system and breast disorders
21. Congenital and familial/genetic disorders
22. General disorders and administration site conditions
23. Investigations
24. Injury and poisoning
25. Surgical and medical procedures
26. Social circumstances
27. Product Issues

The other terms are sorted by dictionary code order.

Appendix H Potentially clinically significant abnormalities criteria

Parameter	PCSA	Comments
Pulse rate (Heart rate)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007
Laboratory		
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Basophils	>0.1 Giga/L	
Monocytes	>0.7 Giga/L	
RBC	≥6 Tera/L	
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	

Appendix I ECG criteria for potentially significant abnormalities - for Phase 2/3 studies (oncology only)

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm	Categories are cumulative
	<50 bpm and decrease from baseline ≥20 bpm	
	<40 bpm	
	<40 bpm and decrease from baseline ≥20 bpm	
	<30 bpm	
	<30 bpm and decrease from baseline ≥20 bpm	
	>90 bpm	Categories are cumulative
	>90 bpm and increase from baseline ≥20bpm	
	>100 bpm	
	>100 bpm and increase from baseline ≥20bpm	
	>120 bpm	
	>120 bpm and increase from baseline ≥20 bpm	
PR	>200 ms	Categories are cumulative
	>200 ms and increase from baseline ≥25%	
	> 220 ms	
	>220 ms and increase from baseline ≥25%	
	> 240 ms	
	> 240 ms and increase from baseline ≥25%	
QRS	>110 ms	Categories are cumulative
	>110 msec and increase from baseline ≥25%	
	>120 ms	
	>120 ms and increase from baseline ≥25%	
QT	>500 ms	
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	>500 ms	
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

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