CONFIDENTIAL INFORMATION

Statistical Analysis Plan (SAP)

Version 1.0

27 February 2025

Study Name	EMPRESS
EudraCT Number	2023-503565-36-00
Protocol Number	MEDOPP459
Protocol Version Date	06-Nov-2023
Title	PREOPERATIVE WINDOW OF OPPORTUNITY STUDY WITH GIREDESTRANT (GDC-9545) OR TAMOXIFEN IN PREMENOPAUSAL WOMEN WITH ER[+]/HER2[-] & KI67≥10% EARLY BREAST CANCER
Sponsor	MEDSIR, Planta 3, Pere IV, 128, 08005, Barcelona MEDSIR MEDICA SCIENTIA INNOVATION RESEARCH
Performed by	MEDSIR, Planta 3, Pere IV, 128, 08005, Barcelona MEDSIR MEDICA SCIENTIA INNOVATION RESEARCH

STATISTICAL ANALYSIS PLAN (SAP)

Signature Page

EudraCT Number: **2023-503565-36-00**

Protocol Number: **MEDOPP459**

[redacted]

Signature:

_____

Date:

_____

Data Science Sr. Specialist

MEDSIR

Barcelona, Spain

Sponsor Signature:

The undersigned hereby declare that they have examined the Statistical Analysis Plan document and agree to its form and content.

Represented by:

Signature: _____	Signature: _____
Date: _____	Date: _____
Name: _____	Name: _____
Title: _____	Title: _____

SAP Revision History:

Version Number	Date	Changes
V1.0	27FEB2025	Initial version

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AI	Aromatase inhibitor
ALT	Alanine transaminase
ALP	Alkaline phosphatase
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
BC	Breast Cancer
CAP	College of American Pathologists
CCCA	Complete cell cycle arrest
CDK4/6i	Cyclin-dependent kinase 4 and 6 inhibitors
CI	Confidence Interval
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal carcinoma in situ
EBC	Early breast cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EoS	End of study
EoT	End of treatment
ER	Estrogen receptor
GCP	Good clinical practice
HER2	Human Epidermal Growth Factor Receptor 2
ICF	Informed consent form
IHC	Immunohistochemistry
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
ITT	Intention-to-treat
LDH	Lactate dehydrogenase
mITT	Modified intention to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events

NCI	National Cancer Institute
QD	Once a day
QoL	Quality of life
PgR	Progesterone receptor
PO	Orally
PR	Partial Response
PT	Preferred term
QT interval	*measure between Q wave and T wave in the heart's electrical cycle*
QTcF	Corrected QT interval using the Fridericia formula
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Severe adverse effect
SoC	Standard of care
ULN	Upper limit of normal

TABLE OF CONTENTS

1 INTRODUCTION

1.1 General

The purpose of this statistical analysis plan (SAP) is to provide a protocol specific description of the statistical analysis that will be performed to produce an integrated clinical/statistical report.

This SAP is based upon the following study documents:

- Protocol latest version: version 3.0 dated 06-11-2023
- eCRF last release version updated: accessed on February 2025

1.2 Type of Study

This is a multicenter, international, open-label, two-arms, one stage, phase II, window of opportunity, clinical trial of Giredestrant (GDC-9545), tamoxifen in patients with ER[+]/HER2[-] & Ki67 ≥10% early breast cancer.

1.3 Study Population

Women ≥18 years of age with well-defined premenopausal status and previously untreated histologically confirmed ER[+]/HER2[-] primary invasive adenocarcinoma of the breast with locally analyzed and centrally confirmed Ki67 ≥10%*, and tumor size ≥1.0 cm in longest diameter by ultrasound.

1.3.1 Target disease

ER[+]/HER2[-] & Ki67 ≥10% early breast cancer.

1.3.2 Inclusion criteria

Patients must meet ALL the following inclusion criteria to be eligible for enrolment into the study:

1. Signed Informed Consent Form (ICF) prior to beginning specific protocol procedures.
2. Aged ≥ 18 years at time of signing ICF.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
4. Women in a well-determined premenopausal status as indicated in the protocol Section 4.1.
5. Histologically confirmed invasive breast carcinoma, with all the following characteristics:

    a. Documented ER-positive tumor in accordance with American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Allison et al., 2020), assessed locally and defined as ≥ 1% of tumor cells stained positive.

    b. Documented HER2-negative tumor in accordance with 2018 ASCO/CAP guidelines (Wolff et al., 2018), assessed locally at baseline.

Note: Diagnostic biopsy taken no more than 8 weeks prior to initiation of study treatment can be used as baseline.

    c. Ki67 score ≥10% analyzed locally and centrally confirmed (Nielsen et al., 2021).

Note: Ki67 will be analyzed locally at the time of inclusion. Patients with basal Ki67 ≥20% will be assessed locally and centrally confirmed retrospectively and patients with 10-19% will be assessed centrally before inclusion.

    d. Tumor size must be ≥1.0 cm in longest diameter by ultrasound as per Response Evaluation Criteria in solid Tumors (RECIST) criteria.

Note: Patients with multifocal or multicentric breast cancer with a at least one tumor lesion ≥1.0 cm in the longest diameter by ultrasound (reference lesion) are also eligible if the two largest lesions have been histologically confirmed in the clinical evaluation and meet pathologic criteria for ER positivity and HER2 negativity.

6. Willingness to provide a primary tumor tissue and blood sample obtained at baseline as well as a post-treatment tumor tissue and blood samples (breast biopsy or from breast surgery).
7. Patient has adequate bone marrow, liver, and renal function:

•Hematological: absolute neutrophil count (ANC) ≥ 1.5 x 109/L (1500/mL), platelet count ≥ 100.0 x109/L, and hemoglobin ≥ 9 g/dL (≥ 90g/L).

Note: The blood counts are to meet the specified criteria without transfusion or growth factor support, unless it is clear that the bone marrow function is adequate and that any aberration has a clear and correctable cause, and the correction undertaken.

•Hepatic: total serum bilirubin ≤ 1.5' institutional upper limit of normal (ULN) (patients with known Gilbert's syndrome: ≤ 3' ULN); alkaline phosphatase (ALP) ≤ 2.5 times ULN; aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 3' times ULN.

•Coagulation: The international normalized ratio (INR) < 1.5' ULN and partial thromboplastin time (PTT or aPTT) < 1.5' ULN (except for patients receiving anticoagulation therapy). For patients receiving warfarin, a stable INR between 2 and 3 is required. For patients receiving heparin, PTT (or aPTT) between 1.5 and 2.5' ULN (or patient value before starting heparin treatment) is required. If anticoagulation therapy is required for a prosthetic heart valve, stable INR between 2.5 and 3.5 is permitted.

•Renal: creatinine clearance ≥ 60 mL/min for patients with creatinine levels above institutional normal.

8. Negative serum pregnancy test result within 14 days prior to initiation of study treatment and a negative urine pregnancy test within 24 hours prior to study treatment initiation.

Note: Premenopausal women age ≥18 years with premenopausal status defined as: estradiol (E2) in the premenopausal range (according to institution parameters) or patient has been menstruating regularly during the 6 months prior to randomization and has not used any form of hormonal contraception or any other hormonal treatments during this time.

Women must remain abstinent and truly abstains from sexual activity (refrains from heterosexual intercourse) or use of locally recognized adequate methods of contraception (described as that with a failure rate <1%) during the length of the study, and to continue its use for 10 days after the last dose of study treatment (for patients taking giredestrant) or 9 months following cessation of therapy (for patients in the tamoxifen arm). They must, as well, agree to refrain from donating eggs during the same period of time.

Examples of non-hormonal contraceptive method with a failure rate of <1% per year (e.g. bilateral tubal ligation, male sterilization and copper intrauterine devices). The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.

9. Patients must be accessible for treatment and follow-up.

10. Participants who are able and willing to swallow, retain, and absorb oral medication.

1.3.3 Exclusion criteria

Patients will be excluded from the study if they meet ANY of the following criteria:

1. Progesterone receptor (PgR)[+] and ER[-] patients.

2. cT4 and/or cN2/3 and/or bilateral BC.

3. Patients who have history of any prior (ipsilateral and/or contralateral) invasive BC or Ductal carcinoma in situ (DCIS). Participants with a history of contralateral DCIS treated by only local regional therapy at any time may be eligible.

4. Evidence of metastatic disease.

5. Previous systemic or local treatment for the primary BC currently under investigation.

6. History of any prior treatment with chemotherapy drugs, aromatase inhibitors (AIs), tamoxifen, selective estrogen receptor down regulator, or cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i).

7. Any invasive malignancy diagnosed within the previous 5 years prior to screening in this study (other than basal cell carcinoma, cervical carcinoma in situ or contralateral DCIS).

8. Known issues with swallowing oral medication, or inability or unwillingness to swallow oral medication.

9. Participants who have a known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including hepatitis (e.g., hepatitis B virus [HBV] or hepatitis C virus [HCV]), current alcohol abuse, cirrhosis, or positive test for viral hepatitis, as defined below:

- Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody [HBcAb]) or HCV antibody. Unless required by local regulations, participants are not required to have HBV, or HCV assessments at screening if these assessments have not been previously performed.
- Participants who test positive for HBcAb are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction is negative for HBV DNA Participants who are positive for HCV serology are eligible only if testing for HCV RNA is negative.

10. Active cardiac disease or history of cardiac dysfunction including any of the following:

- History or presence of symptomatic bradycardia or sick sinus syndrome.
- Resting heart rate < 50 bpm at screening.
- History of angina pectoris, symptomatic pericarditis, myocardial infarction, or any cardiac arrhythmias (e.g.,ventricular, supraventricular, nodal arrhythmias, or conduction abnormality) within 12 months prior to study entry.
- History of documented congestive heart failure (New York Heart Association Class II-IV) or cardiomyopathy.
- QT interval corrected through use of Fridericia's formula (QTcF) >470 ms by at least three ECGs >30 minutes apart.
- History of long or short QT syndrome, Brugada syndrome or known history of corrected QT interval prolongation, or torsades de pointes.
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion.
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophic cardiomyopathy, infiltrative cardiomyopathy, moderate-to-severe valve disease), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of long QT syndrome.

11. Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study.

12. Treatment with strong CYP3A4 inhibitors or inducers within 14 days or 5 drug elimination half-lives (whichever is longer) prior to randomization.

13. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or major upper gastrointestinal surgery including gastric resection.

14. Participants who have a known allergy or hypersensitivity to any of the study drugs or any of their excipients.

15. Participants who are pregnant or breastfeeding or intending to become pregnant during the study or within 10 days after the final dose of giredestrant (GDC-9545), or within 9 months after the final dose of tamoxifen.

Note: Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment and a negative urine pregnancy test within 24 hours prior to study treatment initiation.

16. Patients with renal dysfunction who require dialysis.

17. Participants who have had a serious infection requiring oral or IV antibiotics within 14 days prior to screening or other clinically significant infection (e.g., COVID-19) within 14 days prior to screening.

Note: Participants who have fully recovered from serious or clinically significant infections at least 14 days prior to screening are eligible. If a participant exhibits signs or symptoms of potential COVID-19 infection and there is a

reasonable suspicion of exposure, investigators are to follow the American Society of Clinical Oncology 2020 guidelines or institutional guidelines on testing.

18. Participants who have had a major surgical procedure unrelated to breast cancer within 28 days prior to randomization.

19. Participants who are unable or unwilling to comply with the requirements of the protocol in the opinion of the investigator.

1.4 Study design

This is a multicenter, international, open-label, two-arms, one stage, phase II, window of opportunity, clinical trial aiming to assess changes in tumor cell proliferation as measured by Ki67 expression between baseline and post-treatment (day 15) tumor biopsy samples by central assessment in premenopausal women with ER[+]/HER2[-] & Ki67 ≥10% early breast cancer (EBC).

Note: if post-treatment surgery or biopsy cannot be performed within + 1 day from last day of treatment (that is, on day 15 or the day after), treatment will be extended to 16 days and patients will be able to have surgery or biopsy the following day (be it D15 + 2 days).

After signing informed consent form (ICF) and confirmed eligibility, patients will be randomly assigned in a 1:1 ratio to receive either giredestrant (GDC-9545) 30 mg orally (PO) once a day (QD) or tamoxifen 20 mg PO QD as a single agent. 92 patients are expected to be enrolled in the study and treated for a total of 15 days.

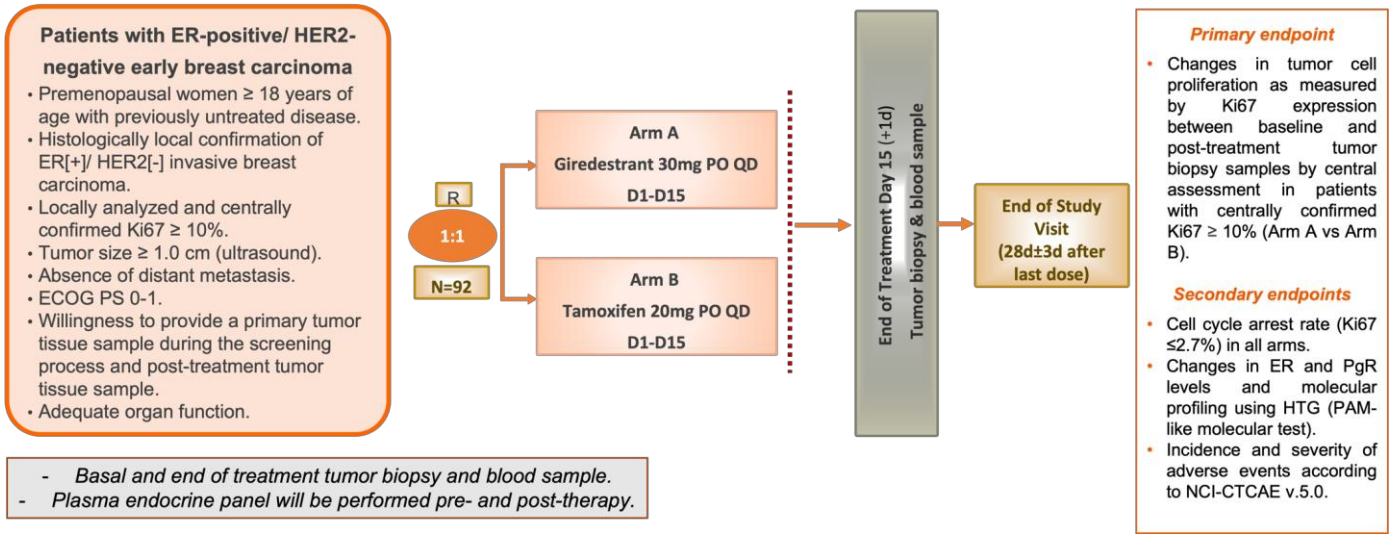

Figure 1. EMPRESS study design. Abbreviations: d: days; ER: Estrogen receptor; PgR: Progesterone receptor; PO: orally; QD: daily; R: randomization.

1.5 Study Schedule

The study will consist of a screening period of up to 28-day, a window-of-opportunity 15-day treatment phase, an End of Treatment visit (EoT) (+ 1 day after the final dose of study treatment) and an End of Study (EoS) visit (28 days +/- 3 days after the final dose of study treatment).

1.5.1 Screening phase

During this phase, patient eligibility is determined, including the documentation of baseline characteristics. This phase will begin once the ICF is signed by the patient.

Patients must have histologically confirmed ER[+]/HER2[-] primary invasive adenocarcinoma of the breast with locally analyzed and centrally confirmed Ki67 ≥10% and tumor size ≥1.0cm in longest diameter by ultrasound.

A Ki67 score ≥10% stained nuclei from the pre-treatment tumor tissue sample is required for eligibility. Ki67 score will be analyzed locally at the time of inclusion. Patients with basal Ki67 ≥20% will be assessed locally and centrally confirmed retrospectively and patients with 10-19% will be assessed centrally before inclusion.

To assess eligibility, HER2, ER and PgR status will be locally determined on the most recent tumor biopsy acquired at baseline prior to beginning of study treatment.

All patients will be required to provide a pre-treatment tumor tissue sample and blood samples during screening, and a tumor biopsy sample and blood samples on Day 15 (+ 1 day) at the end of study treatment. If a diagnostic biopsy was performed maximum 8 weeks prior to initiation of study treatment, it can be used as a baseline sample for the Ki67 assessment. If post-treatment biopsy cannot be obtained within + 1 day from last day of treatment (15 days), treatment will be extended to 16 days and patients will be able to have surgery or biopsy the following day (be it D15 + 2 days).

One re-screening is allowed for patients that were screening failure. Patients have to re-consent Informed Consent Form (ICF) before any study procedure is done. At re-screening, study assessments and procedures can be omitted if were performed during the initial screening period within the specified time frames.

1.5.2 Treatment Phase and End of Treatment visit

The treatment phase is defined as the time between the study entry and the last dose of study treatment received within this trial. After confirming eligibility through the screening process, patients will be scheduled for visit day 1 (D1) of treatment within 48 h after randomization.

In this first visit, medical history, including clinically significant diseases, surgeries, cancer history, and reproductive status will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. Also, in this first visit D1, patients will be given the first dose of treatment and will be instructed how to take giredestrant or tamoxifen orally, daily at their homes during the following 14 days D2 to D15 (to finalize a total of 15 days of treatment).

To assess patient compliance with self-administration of study medication, site study staff will provide patients with detailed instructions and training for the handling and administration of study drugs. Patients will receive and should be instructed to complete a medication diary to record all relevant information during those days.

A second biopsy will be collected at the EoT (on day 15 or day 15 + 1), after last dose of study treatment is taken by the patient in the EoT visit. If a fresh post-treatment biopsy cannot be obtained within + 1 day from last day of treatment, treatment will be extended to 16 days and patients will be able to have surgery or biopsy the following day (be it D15 + 2 days).

If a mandatory procedure described in the protocol falls on a bank holiday and/or weekend, this procedure should be performed on the day before or after the holiday (i.e. within a period of ± 2 working days), with the exception of the post-treatment surgery or biopsy that must be performed on the last day of treatment or 1 day after last day of treatment.

All patients will be closely monitored for safety and tolerability during study treatment. Patients should be assessed for toxicity prior to any study treatment administration; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

1.5.3 Treatment and study discontinuation

If at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue with the protocol therapy, the study treatment should be discontinued and the reason(s) for discontinuation documented in the clinical records of the patient and corresponding case report form (CRF).

Patient's study treatment may continue until one of the following criteria applies:

- Any medical condition or AEs that according to the protocol or in the judgment of the investigator may cause severe or permanent harm or which rule out continuation of study drug.

Note: See detailed criteria for study treatment discontinuation due to toxicity in Section 7.

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Disease progression per investigator's assessment.
- Serious non-compliance with the study protocol.
- Death.
- Pregnancy during study treatment.

- Concomitant use of any other (non-protocol) anti-cancer therapy.
- Lost to follow-up.
- Patient withdraws consent.
- The study site or the Sponsor decides to close the study.

All patients must return for the end of study visit 28 days (+/-3 days) after the final dose of study treatment regardless of the reason for treatment discontinuation. Patients who experience disease progression or unacceptable toxicity will be treated as per local practice after the EoS visit. If a patient discontinues treatment before the EoT visit (that is, before finalizing 15 days of treatment), the collection of tissue and blood samples will be discussed with the study medical monitor and will only be collected if feasible and as soon as possible (from a breast biopsy or breast surgery).

Patients have the right to withdraw from the study at any time for any reason. Should a patient decide to withdraw, all efforts should be made to complete and report the observations as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. Patients deciding to prematurely discontinue study treatment should be asked if they still can be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the CRF.

The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, AEs, and treatment failure after a prescribed procedure, protocol violation, administrative reasons, or for other reasons. An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

1.5.4 End of study visit

Patients will attend the clinic again for an EoS visit 28 days (+/- 3 days) after last dose of study treatment is taken.

All AEs related to investigational medicinal product (IMP) will be followed up by the investigator until the event or its sequelae has resolved to baseline grade or better, the event is considered as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be done to follow-up all serious adverse events considered to be related to study drug or trial-related procedures until an outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. All pregnancies reported during the study should be followed until pregnancy outcome.

The EoS is defined as the last patient last visit, which takes place 28 days (+/- 3 days) after the last study dose is taken (or if patient ends treatment due to progression or any other reason listed in the previous section, or until premature termination of the study). This will be the last data collection point, and the last patient visit.

In addition, the Sponsor reserves the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or seriousness of AEs in this or other studies indicates a potential health risk to patients.
- Patient enrollment is unsatisfactory and/or excessively slow.
- Data recording is inaccurate or incomplete.
- Poor protocol adherence.
- Non-compliance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP).

1.6 Sample Size

The analysis will compare absolute changes for Ki67 expression between baseline score and the evaluation after the treatment. The sample size was based on a superiority contrast between two study arms analyzed with a two-sided t-test set at 0.05 alpha level. We assumed a 70% mean in giredestrant (GDC-9545) Arm vs. 50% mean in tamoxifen

with a 29% common standard deviation, according to the results observed (Dowsett, Smith, et al., 2005). We planned 34 patients per arm to attain an 80% power.

The final analysis will be conducted with unpaired Wilcoxon test because of the non-asymptotic distribution of data. We assumed that asymptotic efficiency of Wilcoxon test relative to the t-test, never falls below 0.86 (Jr & Lehmann, 1956). In addition, we expect a 10% dropout rate. So, 46 patients per arm will be finally recruited. We used the R software version 4.0.2. released on 2020-06-22 ("pwr").

2 STUDY OBJECTIVES

2.1 Primary objective

To assess changes in tumor cell proliferation as measured by Ki67 expression between baseline and post-treatment tumor biopsy samples by central assessment in patients with centrally confirmed Ki67 ≥10% (Arm A vs Arm B).

2.2 Secondary Objectives

- To measure complete cell cycle arrest (CCCA) in all arms, defined by Ki67 ≤2.7% in post-treatment sample.
- To analyze changes in ER and PgR levels, and molecular profiling using HTG.
- To evaluate toxicity according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5.0.

[redacted]

2.4 Endpoints definitions

Primary endpoint:

Changes in tumor cell proliferation as measured by Ki67 expression between baseline and post-treatment tumor biopsy samples by central assessment in patients with centrally confirmed Ki67 ≥10% (Arm A vs Arm B).

Secondary endpoints:

- CCCA in all arms, defined as the percentage of participants with centrally assessed Ki67 scores ≤2.7% stained nuclei upon treatment (post-treatment sample).
- Changes in markers (such as ER and PgR levels) and molecular profiling using HTG (PAM-like molecular test).
- Incidence and severity of adverse events (AEs), with severity determined in accordance with NCI-CTCAE v.5.0.

[redacted]

2.5 Safety endpoints

Safety endpoints:

- Drug Administration:
  - Relative dose intensity: $RDI = \left(\frac{DDI}{SDI}\right) \times 100$
    - DDI = Delivered dose intensity
    - SDI = Standard dose intensity
  - Duration of treatment: It is defined as the period of time from treatment initiation to the end of treatment.

- Duration of follow-up: It is defined as the period of time from treatment initiation to the end of study follow-up visit date or the latest date available.
- Percentage of patients with dose reduction: It is defined as the proportion of participants with dose reduction relative to the number of patients in the analysis set. The reasons for dose reduction will be also reported.
- Percentage of patients with dose delays: It is defined as the proportion of participants with dose delays or temporary interruption relative to the number of patients in the analysis set. The reasons for dose delays will be also reported.
- Percentage of patients discontinued: It is defined as the proportion of participants discontinued to any cause relative to the number of patients in the analysis set. The reasons for study discontinuation will be also reported.

- Adverse events:

The incidence of AEs, TEAES, TEAES grade ≥ 3, related TEAES, AESI, SAEs, TEAES leading to dose reduction, dose delay, permanent discontinuation or death will be summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and graded using the NCI-CTCAE v.5. Other safety parameters such laboratory parameters, the extent of exposure to study medication, concomitant medications, vital signs, physical examination, reason for treatment reductions, delays, discontinuations, and reason for follow-up discontinuations will be summarized.

- Laboratory parameters:
  - Hematology parameters
  - Biochemistry parameters
- Additional safety parameters:
  - Concomitant medications
  - Vital signs
  - Physical examination
  - ECOG performance status

3 ANALYSIS SETS

Modified intention to treat (mITT) set

All randomly assigned patients that accomplish major selection criteria (Central Ki67 ≥ 10%), with ≥ 14 days of treatment*, and the central Ki67 evaluated at baseline and at most on the day after the completion of treatment Subjects will be analyzed according to treatment allocated. The mITT set will be used for primary and secondary efficacy analysis.

*One day of deviation from the 15 days of treatment indicated for the main objective will be accepted.

Intention-to-treat (ITT) analysis set

All patients randomized. Subjects will be analyzed according to treatment allocated. The ITT set will be used for supportive efficacy analyses.

Per protocol analysis (PP) set

All randomly assigned patients that accomplish major selection criteria, with Ki67 evaluable values at baseline and after the treatment, with a minimum exposure to the drugs assigned in the randomized arm, and without major protocol deviations. Criteria for determining the "per protocol" group assignment would be established by the Steering Committee before the statistical analysis begins. Subjects will be analyzed according to treatment received. The PP set will be used for supportive efficacy analyses. This analysis will only occur if this set differs by ≥ 10% from the mITT set.

Safety analysis set

Includes all patients who received at least one dose of the study drug. Subjects will be analyzed according to treatment received. The safety set will be used for analyses of safety endpoints.

[redacted]

4 STATISTICAL METHODS

4.1 General Methodology

The statistical analysis will be conducted following the principles as specified in International Conference on Harmonization (ICH) Topic E9 (CPMP/ICH/363/96). The significance level will be α=0.05 for all tests. As an exploratory study, multiple testing without adjustment of the significance level is considered acceptable.

Definition of baseline: For each safety or efficacy parameter, the last valid assessment made before first study drug administration will be used as the baseline for all analyses of that safety or efficacy parameter unless otherwise specified.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), median, minimum, maximum, and first and third quartiles, unless otherwise stated. Where data are collected over time, both the observed data and change from baseline will be summarized at each time point.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, and first and third quartiles will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Percentages will be presented to one decimal place. A percentage of 100% will be reported as 100.0%. Unless otherwise stated, percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report (e.g., clinical study report) will describe frequencies only.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<.001".

Confidence intervals will be presented to one more decimal place than the raw data. A two-sided significance level of 95% will be used for confidence intervals.

For binary endpoints, the 95% confidence intervals (CIs) will be constructed based on Clopper-Pearson.

The Kaplan-Meier method will be used to estimate the time to event function, the median of time to event, minimum, maximum and the 95% confidence interval of the same will be calculated. These confidence intervals will be calculated based on the Greenwood method. Number of patients included in the analysis and total number of events will be shown.

All scores and change from baseline will be summarized in terms of the number of observations, mean, standard deviation, median, range and interquartile range.

All report outputs will be produced using SAS® version 9.4 version or posterior in a secure and validated environment under SAS Enterprise Guide v8.3 or later user interface. All report outputs will be provided to the Sponsor in rtf format.

4.2 Subject Disposition

Descriptive statistics will be provided for the following:

- Overall number of subjects in the screening set, the number of patients eligible to participate in the study, and number of screening failures.
- Number and percent of subjects in each of the analysis sets.
- Number and percent of subjects excluded from each of the analysis sets along with reason for exclusion.
- Listing of subjects excluded from each of the analysis sets along with reason for exclusion.
- Listing of protocol deviations.

- Number and percent of subjects from End of Treatment.
- Number and percent of subjects form End of Study with reasons.

4.3 Baseline Characteristics

Descriptive statistics will be provided for the following baseline characteristics:

- **Demographic data**: sex, age, ethnicity, country; for women, pregnancy test, contraception methods and/or menopausal status; and for men, contraception endpoints;
- **Medical history**: habits (smoking, alcohol and drugs consumption), significant diseases, surgeries, other cancers, previous therapies and procedures; Breast cancer history: study tumor characteristics, previous treatment for breast cancer (radiotherapy and/or antineoplastic);
- **General assessment at baseline**: physical examination and vital signs endpoints; ECOG performance status, and 12-Lead ECG; Molecular biomarkers, Coagulation endpoints, Haematology and Biochemistry parameters; Tumor assessment before the study treatment, including tumor sample and radiologic imaging; and
- **Concomitant medication** prior to screening visit.

All parameters will be described according to their characteristics, as follow:

- **Categorical variables** will be summarized using number, frequencies and percentages.
- **Continuous variables** will be summarized using measures of central tendency and dispersion: mean, standard deviation, median, 25% and 75% percentiles (Q1 and Q3) and extreme values (minimum and maximum).

4.4 Efficacy Analysis

Primary efficacy analysis will be reported for either mITT, ITT and PP sets.

Second efficacy analysis will be reported for mITT set.

4.4.1 Primary Efficacy Endpoint

The change in tumor cell proliferation as measured by Ki67 expression between baseline and the post-treatment tumor biopsy samples by central assessment.

The primary analysis will be done for the mITT analysis set. We only will analyse observed valid cases (observed-cases method).

The global null hypothesis is that the giredestrant (GDC-9545) does not differ from tamoxifen treatment group in the mean percentage of absolute difference in Ki67 between baseline score and after the treatment. The alternative hypothesis is that the giredestrant (GDC-9545) differs from the tamoxifent treatment group.

The test of the null hypothesis is based on a two-sided Wilcoxon unpaired test set at 0.05 alpha level. It includes treatment as a factor. The response variable is the absolute difference in Ki67 score after the treatment. We propose declaring the superiority of giredestrant (GDC-9545) therapy if shown to be superior in this analysis.

We will estimate the 95% confidence intervals (CI) for the mean and median of absolute difference between baseline and the post treatment evaluation in each study arm. The 95% confidence intervals (CI) for the mean and median difference between treatments are estimated by the T-Test and Hodges–Lehmann estimator, respectively.

Individual baseline and post-treatment Ki67 scores will be summarized with dot plots linking with a line the observations of the same patient. Absolute and relative change between baseline and post-treatment will be summarized with waterfall and bar plots.

4.4.1.1 Missing data imputation methods

The values of Ki67 could be missing for patients without valid analytic values or withdrawal. Missing values for primary endpoint will be managed with three methods:

a) Observed case imputation: Only observed valid cases are analyzed.
b) Last observation carried forward: Missing value are replaced by the last value observed before.
c) The standard multiple imputation performed in three steps: (1) the imputation of non-monotone missing data using MCMC. A total of 10 complete datasets are generated within this step; (2) the imputation of monotone missing data with regression models; (3) the calculation of endpoint estimates, standard errors and p-values for each dataset; and (4) the combination of all dataset results by Rubin's rules.

4.4.1.2 Supportive analyses for primary efficacy endpoint

The primary endpoint analysis will be repeated for the PP and ITT set as described in the previous section. For ITT analysis the missing values for Ki67 after the treatment are imputed with baseline Ki67 scores based on the last observation carried forward principle (0 score in absolute difference of Ki67). For PP analysis only observed valid cases will be analyzed.

Additionally, the following supportive analyses will be performed (Table 6. Planned analyses for the primary endpoint.):

a) The Ki67 score after two weeks of treatment will be adjusted by baseline Ki67 scores. The analysis will be done for the mITT, ITT and PP analysis set (as appropriate). We only will analyze observed valid cases for mITT and PP analysis set. Alternatively, the missing management method for ITT analysis will be the multiple imputation.

The test of the null hypothesis is based on a linear regression model which includes treatment as a factor and baseline Ki67 score as covariate. The response variable is the Ki67 score after the treatment. The transformed values of the Ki67 score are assumed to be a linear function of the treatment as:

$$\mathbf{Y = \beta 0 + \beta 1 X1 + \beta 2 X2}$$

where

Y = The Ki67 score after the treatment,

β0 denotes intercept,

β1 denotes the treatment effect,

X1 refers to the treatment groups (Giredestrant (GDC-9545) and tamoxifen),

β2 denotes the Ki67 baseline score effect,

X2 refers to the Ki67 baseline score.

The parameterization method is based on a reference group (tamoxifen). The p-values and 95% CI are estimated by the Wald method. The 95% CI will be also reported back transformed.

b) The relative percentage of change between baseline and the post treatment evaluation in each patient will be calculated using the baseline and post-treatment scores divided by baseline scores per 100. The 95% CI for the arithmetic and geometric mean in each arm will be estimated with T-Test.

The geometric mean will be estimated using the log values for the relative percentage of change. The log-transformation is designed for non-negative values, so we will add a constant to the individual values of relative percentage change before applying the transformation. The 95% CI for the geometric mean will be reported back transformed using the anti-log scale and subtracting the constant. The analysis will be done for the mITT, ITT and PP analysis set (as appropriate). We only will analyze observed valid cases for mITT and PP analysis set. Alternatively, the missing management method for ITT analysis will be the multiple imputation.

Table 1. Planned analyses for the primary endpoint

ID	Set	Analysis sets	Main estimate and (Imputation Method)	Type of analysis
1	mITT	Patients excluded: -Central Ki67 < 10% or not evaluable at baseline. -<14 days of treatment. -Without the Ki67 central evaluation at baseline and after at most on the day after the completion of treatment.	**Central Ki67 score** Difference between baseline and post treatment evaluation. (Observed case)	Primary -Willcoxon unpaired -95% CI T-test -95% CI HL
2	ITT	All patients randomized regardless of IEs are included (Treatment policy strategy).	**Central Ki67 score** Difference between baseline and post treatment evaluation. (Last observation carried forward)	Supportive -Willcoxon unpaired -95% CI T-test -95% CI HL
3	PP	Patients excluded: -Central Ki67 < 10% or not evaluable at baseline. -Without the Ki67 central evaluation after the treatment -Patients with other major deviations in accordance steering committee.	**Central Ki67 score** Difference between baseline and post treatment evaluation. (Observed case)	Supportive -Willcoxon unpaired -95% CI T-test -95% CI HL
4	mITT	See above ID nr. 1	**Central Ki67 score** Ki67 score after the treatment adjusted by baseline score. -Box-cox transformation (Observed case)	Supportive -Linear regression (Wald test) adjusted by baseline scores
5	ITT	See above ID nr. 2	**Central Ki67 score** Ki67 score after the treatment adjusted by baseline score. -Box-cox transformation (Multiple imputation)	Supportive -Linear regression (Wald test) adjusted by baseline scores
6	PP	See above ID nr. 3	**Central Ki67 score** Ki67 score after the treatment adjusted by baseline score. -Box-cox transformation (Observed case)	Supportive -Linear regression (Wald test) adjusted by baseline scores
7	mITT	See above ID nr. 1	**Central Ki67 score** % of change between baseline and post treatment evaluation. (Observed case)	Supportive -95% CI for arithmetic and geometric means in each arm
8	ITT	See above ID nr. 2	**Central Ki67 score** % of change between baseline and post treatment evaluation. (Multiple imputation)	Supportive -95% CI for arithmetic and geometric means in each arm
9	PP	See above ID nr. 3	**Central Ki67 score** % of change between baseline and post treatment evaluation. (Observed case)	Supportive -95% CI for arithmetic and geometric means in each arm

4.4.2 Secondary Endpoints and Subgroup Analysis

The secondary efficacy endpoints will be done for the mITT analysis set. We only will analyze observed valid cases.

For quantitative measures (Ki67, ER, PR, and other molecular markers) the mean, median, geometric mean, standard deviation, interquartile range, and range will be reported as appropriate per study arm and visit. Summary statistics for the absolute and relative change between baseline and post-treatment will be also reported.

Individual baseline and post-treatment scores in quantitative measures will be summarized with dot plots linking with a line the observations of the same patient. Absolute and relative change between baseline and post-treatment will be summarized with waterfall and bar plots.

The difference between baseline and post-treatment evaluation will be compared in each arm with Wilcoxon paired test. We will estimate the 95% confidence intervals (CI) for the mean and median.

The difference between study arms at baseline and after the treatment will be compared with Wilcoxon unpaired test. We will estimate the 95% confidence intervals (CI) for the mean and median difference between treatments with T-Test and Hodges–Lehmann estimator, respectively. The comparison of quantitative score after two weeks of treatment in each arm will be adjusted by baseline scores based on linear regression.

For qualitative measures (CCCA [Ki67≤2.7%] after the treatment) we will calculate the number and proportion of patient achieving the cut-off criterion. We will estimate the proportions with the 95% Clopper-Pearson confidence intervals. The between arms comparison will be conducted with logistic regression models. Factor estimates, odds ratios, corresponding 95% confidence intervals, and p-value will be presented. P-values and 95% confidence intervals will be based on Wald test.

The comparison of primary and secondary endpoints between patient and molecular characteristics will be conducted if considered appropriate. The quantitative endpoints will be analyzed with linear regression based on Wald test. The binary endpoints will be analyzed with logistic regression models. Factor estimates, odds ratios, corresponding 95% confidence intervals, and p-value for applicable test statistics will be presented. P-values and 95% confidence intervals will be based on Wald test.

For all secondary analyses, we will use two-sided p-values with alpha ≤ 0.05 level of significance and 95% confidence intervals.

4.5 Safety analysis

Safety data will be analyzed in safety analysis set. All safety measures will be described in each arm. We will summarize adverse events and adverse events (AE) of special interest (AESI), premature withdrawal from study medication, laboratory parameters, exposure to study medication, concomitant medications, vital signs, ECOG performance status, and physical examination.

The number and percentage of AEs and SAEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT). Additional summaries by frequency tables will also be provided for the AEs. Patients who died will be listed together with the cause of death.

Laboratory parameters, hematology and biochemistry, will be presented in shift tables of NCI-CTCAE grade at baseline versus worst grade during treatment.

Other safety variables, such as exposure to study medication, ECOG performance status, concomitant medications, vital signs, and physical examination, will be analyzed in a similar way. Frequency tables will summarize the exposure of study medication.

4.5.1 Drug administration

The drug administration endpoints are:

- Duration of treatment (months): $\frac{(date\ of\ last\ medication)-(date\ of\ first\ medication\ administration)+1}{30.25}$, when the date of last medication is known and complete.

- Duration of follow-up (months): $\frac{(date\ of\ last\ visit)-(date\ of\ baseline)+1}{30.25}$, where last visit date could be the last day of follow-up, or date of death, or date of last visit before a dropout.

- Relative Dose intensity: $\frac{Cumulative\ dosage\ received\ (mg/Kg)}{Product\ of\ the\ assigned\ dose\ (mg/kg)}$, based on the number of doses the patient was scheduled to receive during the patient's treatment period.

- Dose reduction: Patients with at least a dose reduction in the study.
- Dose delay: Patients with at least a dose delay in the study.
- Discontinued patients: Patients who discontinued the study.

These parameters will be summarized using measures of central tendency and dispersion; mean, median, standard deviation, 25% and 75% percentiles (Q1 and Q3) and extreme values (minimum and maximum).

4.5.2 Adverse Events

The adverse events will be tabulated per arm containing the number and percentage of subjects with the following:

- Subjects with at least one Adverse Event; and number of reported adverse events
- Subjects with at least one AE of special interest (AESI); and number of AESI
- Subjects with at least one Serious Adverse Events (SAEs); and number of SAEs
- Subjects with at least one AE related to the treatment; and number of AE related to the treatment
- Subjects with at least one SAE related to the treatment; and number of SAE related to the treatment

- Subjects who died due to SAEs; and number of SAEs that caused death
- Subjects that dropout due to SAEs; and number of SAEs that caused discontinuation
- Subjects with at least one treatment-emergent adverse event (TEAE); and number of reported TEAE. Adverse events starting or worsening during treatment phase will be considered as TEAEs.
- Subjects with at least one TEAE Grade ≥ 3; and number of reported TEAE Grade ≥ 3.

The AEs will be also summarized according to the primary SOC and within each SOC, by PT according to the Medical Dictionary for Regulatory Activities (MedDRA). The duration of AE will be calculated as follows:

- Duration of an AE (days): $(date\ of\ resolution) - (start\ date) + 1$ when both end and start dates of AE are known and complete.

Missing data imputation methods

When data is not completed it will be considered as:

- Day 15 if day is missing
- Day 1 and month July if day and month are missing

In the event of not being able to allocate an AE, it will be considered as being a TEAE. Any missing information will be considered as being the worst case scenario (serious and treatment related).

4.5.3 Laboratory parameters

Laboratory parameters (Hematology and Biochemistry) will be presented as shift tables of NCI-CTCAE grade at baseline versus worst grade during treatment. Shift tables display the number and percentage of subject within each grade/category of baseline and the shift to worst grade/category during the treatment.

Hematology tests will include analysis of hemoglobin, hematocrit, red blood cell count, platelet count, and WBC count with differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

Biochemistry test will include sodium, potassium, calcium, chloride, magnesium, phosphorus, urea, blood urea nitrogen (BUN), urate, total protein, albumin, ALP, AST, ALT, GGT, LDH, direct and total bilirubin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, FSH, Estradiol, glucose and creatinine.

Coagulation test will include international normalized ratio (INR), Activated partial thromboplastin time (aPTT) and prothrombin time.

Serum and urine pregnancy test results will be depicted.

4.5.4 Additional safety variables

Additional safety variables are dived into five categories; concomitant medication (CM), vital signs, physical examinations, 12 lead electrocardiogram (ECG) and ECOG performance status.

Concomitant medications will be coded according to WHO Drug dictionary available at time of database lock. The number and percentage of patients with at least one dose of medication and the number of CMs by groups will be reported.

Vital signs and physical examinations endpoints will be summarized. The vital signs parameters are: height (cm), weight (Kg), Body Mass Index (BMI), respiratory rate (bpm), heart rate (bpm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and body temperature (ºC). The physical examinations parameters are: head, eyes, ears, nose and throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological evaluations.

Overall assessment of 12 lead ECG will be presented.

ECOG performance status will be also presented as shift tables from baseline to worst value during treatment. The number and percentage of patient in each ECOG category will be tabulated for every evaluation.

5 PLANNED ANALYSES

The following analyses will be performed for this study:

5.1 Interim analysis

No interim analysis planned for this study.

5.2 Final analysis

After the database lock

6 CHANGES OF ANALYSIS FROM PROTOCOL

NA.

7 DEVIATIONS FROM SAP

NA.

8 LIST OF TABLES, LISTINGS, FIGURES

A complete list of tables, listings and figures (TLFs) will be given in a separate document which can be updated without updating the SAP. The list will serve as a reference for both the Sponsor, the trial statistician and the statistical programmer and includes the totality of statistical output to be produced.

All statistical output will identify the underlying analysis sets and indicate the number of patients/events in this set (N) and the number of patient/events actuals contributing to the output (n). All statistical output will be presented per treatment (if applicable).

All patient listings will contain additionally to the patient identification the analysis set and the treatment.