Clinical Study Protocol (CSP)

PREOPERATIVE WINDOW OF OPPORTUNITY STUDY WITH GIREDESTRANT (GDC-9545) OR TAMOXIFEN IN PREMENOPAUSAL WOMEN WITH ER[+]/HER2[-] & KI67 ≥10% EARLY BREAST CANCER

(<The EMPRESS Study>)

Study Code: MEDOPP459

EU CT #: 2023-503565-36-00

***Clinicaltrials.gov* #:** NCT05659563

Investigational Medicinal Product(s): Giredestrant (GDC-9545), tamoxifen

CSP Version, Date: 3.0, 06-Nov-2023

CSP Review History

1. CSP version, date: 1.0, 27-Jan-2023 (Initial Submitted CSP Version)
2. CSP version, date: 2.0, 27-Apr-2023 (**Initial Approved CSP Version**)
3. CSP version, date: 3.0, 06-Nov-2023

SPONSOR'S SIGNATURE PAGE

Study title: PREOPERATIVE WINDOW OF OPPORTUNITY STUDY WITH GIREDESTRANT (GDC-9545) OR TAMOXIFEN IN PREMENOPAUSAL WOMEN WITH ER[+]/HER2[-] & KI67 ≥10% EARLY BREAST CANCER (<The EMPRESS Study>)

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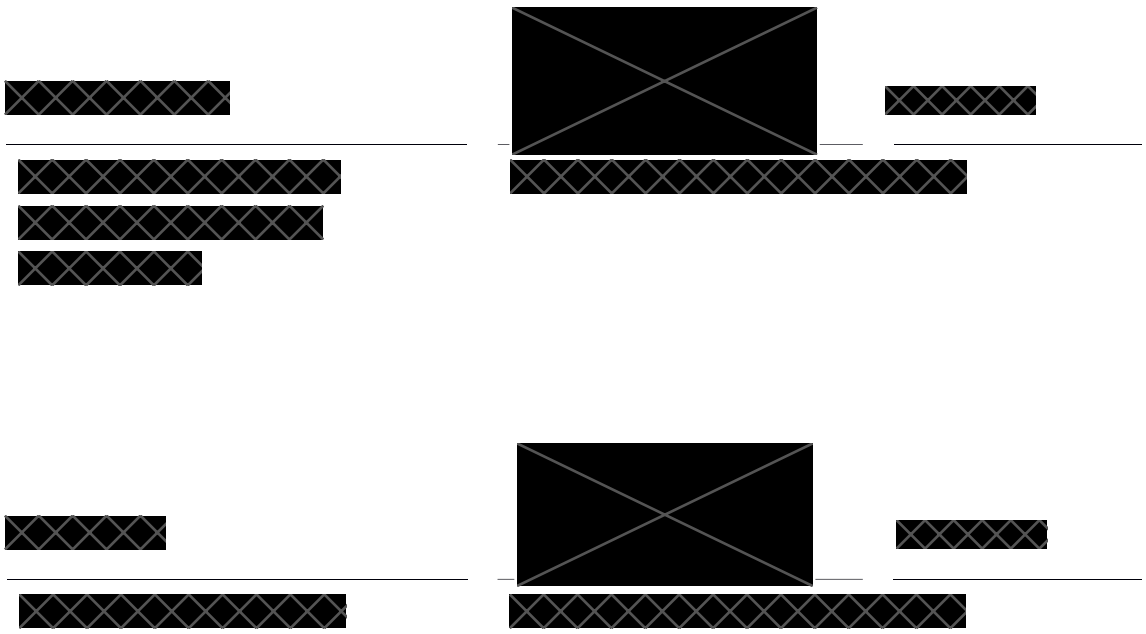

KEY CONTACT DETAILS

Sponsor

Name:	[redacted]
Contact Name:	[redacted]
Address:	[redacted]
Phone/Fax:	[redacted]
E-mail:	[redacted]

Sponsor's Medical Scientist

Name:	[redacted]
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]
E-mail:	[redacted]

Sponsor's Safety Risk Management

Name:	Medica Scientia Innovation Research (MEDSIR)
Address:	Torre Glòries, Av. Diagonal 211, Planta 27, 08018 Barcelona (Spain)
Phone:	+ 34 932 214 135
Fax:	+ 34 932 992 382
E-mail:	EMPRESS_pharmacovigilance@medsir.org

Study Principal Investigator

Name:	[redacted]
Email:	[redacted]
Position:	[redacted]
Institution:	[redacted]

Study Co-Principal Investigator

Name:	[redacted]
Email:	[redacted]
Position:	[redacted]
Institution:	[redacted]

STEERING COMMITTEE

Name	Role
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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DECLARATION OF INVESTIGATORS

Study title: PREOPERATIVE WINDOW OF OPPORTUNITY STUDY WITH GIREDESTRANT (GDC-9545) OR TAMOXIFEN IN PREMENOPAUSAL WOMEN WITH ER[+]/HER2[-] & KI67 ≥10% EARLY BREAST CANCER (<The EMPRESS Study>)

Study Code: MEDOPP459

I have received, reviewed and understood the following:

a) Clinical Study Protocol (CSP) Version, Date: 3.0, 06-Nov-2023.

b) Investigator's Brochure (IB) of giredestrant (GDC-9545) and Summary of Product Characteristics (SmPC) for tamoxifen with details of clinical and nonclinical data that are relevant to the study of the products in human subjects.

- I have been adequately informed about the development of the investigational products to date. I will confirm the receipt of updated IB and SmPCs. I have read this study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol.
- I fully understand that any changes instituted by the investigator(s) without previous agreement with the Sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the wellbeing of the patients). I am aware that I cannot deviate from or apply changes to the protocol without prior approval or the favorable opinion of the Institutional Review Board (IRB) or Ethics Committee (EC) and/or before Sponsor's agreement to avoid immediate risk to the trial patients. If this occurs, I agree to inform the Sponsor as to the deviation or changes in writing and their reasons, as soon as possible.
- I will not enroll the first patient in the study until I have received approval from the appropriate IRB/EC and until all legal and regulatory requirements in my country have been fulfilled.
- The study will be conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and its amendments, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines (ICH E6(R2) GCP) and applicable regulations and laws.
- I agree to obtain, in the manner described in this protocol and in (ICH E6(R2) GCP), signed informed consent form (ICF) by the patient or witnessed verbal ICF to participate for all patients whose participation in this study is proposed to and before any patient's study specific procedure is done.

- I will ensure that the study drug(s) supplied by the Sponsor are being used only as described in this protocol and in the latest version of the IB.
- I am aware of the requirements for the correct reporting of safety events according to the protocol, and I commit to document and to report such events as required by the Sponsor and in accordance with Health Authority Regulatory requirements.
- I agree to supply – upon request – the Sponsor or Sponsor's representative with evidence of current laboratory accreditation, the name and address of the laboratory, and a list of normal values and ranges.
- I agree with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals.
- I agree to keep all source documents and case report forms as specified in the relevant sections of this protocol.
- I will provide all required Regulatory Authority forms, up-to-date curriculum vitae of myself, sub-investigators and of any member of my study team (if requested) before the study starts, which may be submitted to regulatory authorities.
- I am aware of the possibility of being audited by the Sponsor or its delegate or inspected by regulatory authorities for the performance of this study. I will permit monitoring, auditing and inspection and provide direct access to source data/documents and reports for these purposes.
- Furthermore, I confirm herewith that the Sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

Name: _____

Signature: _____ Date: _____

CLINICAL STUDY PROTOCOL (CSP) SYNOPSIS

CSP Title:	Preoperative window of opportunity study with giredestrant (GDC-9545) or tamoxifen in premenopausal women with ER[+]/HER2[-] & Ki67 ≥10% early breast cancer (EBC).
CSP Short Title:	The EMPRESS Study
Study Code:	MEDOPP459
EU CT #:	2023-503565-36-00
Clinicaltrials.gov #:	NCT05659563
Trial Design:	This is a multicenter, international, open-label, two-arms, one stage, phase II, window of opportunity, clinical trial.
Investigational Medicinal Products:	Giredestrant (GDC-9545), tamoxifen.
Target Disease:	ER[+]/HER2[-] & Ki67 ≥10% EBC.
Patients:	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. Patients with distant metastatic disease are not eligible. Patients diagnosed with multifocal or multicentric breast cancer with at least one lesion ≥1.0 cm in the longest diameter by ultrasound (reference lesion) are also eligible if the largest tumor lesions have been histologically confirmed in the clinical evaluation and meet pathologic criteria for ER positivity and HER2 negativity. The reference lesion will be used to assess changes in tumor cell proliferation as measured by Ki67 expression. Patients must have an adequate organ function. Patients must agree to provide a primary tumor tissue sample and a blood sample obtained at baseline as well as a post-treatment tumor tissue and a blood sample (breast biopsy or from breast surgery, which will be performed either on the last day of treatment or the following day).

	**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.*
Number of patients:	92
Selection criteria:	**Inclusion criteria** Patients will be included in the study only if they meet ALL the following criteria: 1. Signed Informed Consent Form (ICF) prior to beginning specific protocol procedures. 2. Age ≥18 years at time of signing ICF. 3. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. 4. Women with a well-determined premenopausal status as indicated in the protocol. 5. Histologically confirmed invasive breast carcinoma, with all the following characteristics: a. Documented ER[+] 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[-] 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 at least one tumor lesion ≥1.0 cm in the longest diameter by ultrasound (reference lesion) are also eligible if the two largest tumor 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 a blood sample (breast biopsy or breast surgery).
7. Patient has adequate bone marrow, liver, and renal function:
   - Hematological: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1500/mL), platelet count ≥ 100.0 x10^9/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 abstain 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.

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.

Exclusion criteria:

Any patient meeting ANY of the following criteria will be excluded from the study:

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 breast cancer 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 breast cancer 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 in the protocol.
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 hypertrophy 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.
Study objectives:	**Primary objectives** • 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). **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]

	• [redacted] [redacted] [redacted]
Study Endpoints:	**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 endpoint** • 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] [redacted] [redacted] [redacted]
Study treatment:	Investigational Medicinal Products (IMPs) will be giredestrant (GDC-9545) (test product) and tamoxifen (comparator). Eligible participants will be randomly assigned in a 1:1 ratio to either Arm A (treatment with giredestrant [GDC-9545]) or Arm B (treatment with tamoxifen). • Giredestrant (GDC-9545): 30mg, orally (PO), daily (QD) on days 1-15. • Tamoxifen: 20mg, PO, QD on days 1-15. Patients will be treated for a total of 15 days. *Note: If post-treatment surgery or biopsy cannot be performed within + 1 day from last day of treatment (15 days), treatment will be extended*

	to 16 days and surgery or biopsy will be performed on the following day.
Study Procedures, Efficacy, and Safety Assessments:	**Screening period** After signing the ICF and after confirming eligibility through the screening process, patients will be biopsied to confirm Ki67 score. *Note: 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.* **Patient visits** After confirming eligibility through the screening process, patients will be scheduled a visit for day 1 (D1) of treatment within 48 h after randomization. This visit must be scheduled as soon as possible upon reception of Ki67 score result (maximum 8 weeks between biopsy and the scheduled C1D1). 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, for visit day 1 (D1) of treatment, patients will be given the first dose of treatment and will be instructed how to take giredestrant (GDC-9545) or tamoxifen orally, daily at their homes during the following 14 days (D2 to D15, to finalize a total of 15 days of treatment). Interruptions or delays due to any reason should be discussed with the medical monitor. 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 end of treatment (EoT) after last dose of study treatment is taken by the patient. If post-treatment surgery or biopsy cannot be performed within + 1 day from last day of treatment (that is, on Day 15 or Day 15 +1), treatment will be extended

to 16 days and surgery or biopsy will be performed on the following day (be it Day 15 + 2 days).

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

Assessments

- Mandatory tumor tissue biopsy samples will be collected before the start of treatment (up to a maximum of 8 weeks before the first dose of study drug). If a diagnostic biopsy was performed maximum 8 weeks prior to study treatment initiation, it can be used as a baseline sample for the Ki67 assessment. Additional biopsy will be taken at the EoT (+ 1 day) after the last dose of study drug. If post-treatment surgery or biopsy cannot be performed within + 1 day from last day of treatment (15 days), treatment will be extended one extra day and patients will be able to have surgery or biopsy the following day (be it D15 + 2 days). Mandatory liquid biopsy samples will be obtained before the start of treatment (up to a maximum of 14 days before the first dose of study drug) and, if possible, at the same timepoint as baseline hematological laboratory assessments. Post-study treatment liquid biopsy samples will be taken at the same timepoint, if possible, as post-study treatment tumor biopsies.
- Visits scheduled for D1 and EoT will include an evaluation of vital signs (including: measurements of weight, respiratory rate, heart rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature), physical examination (a complete physical examination should include the evaluation of head, eye, ear, nose, and throat; cardiovascular; dermatological; musculoskeletal; respiratory; gastrointestinal; and neurological systems), and analysis of laboratory results (including biochemical and hematological analysis, as well as pregnancy test). EoT visit will also include a review of the patient diary and new or worsened clinically significant abnormalities.
- ECOG Performance status will be completed at screening and as specified in the schedule of activities.

- Known breast ultrasound result will be mandatory at screening (prior to randomization).
- Baseline staging to document absence of metastatic disease should be performed as per institutional practice, in alignment with national guidelines and as clinically indicated, in patients where there may be a reasonable suspicion of advanced disease (e.g., clinically positive axillary lymph nodes, signs and symptoms). If performed, it must be within 28 days prior to randomization and reports of these examinations must be available. Examination type for tumor staging is at the discretion of the investigator and includes, for example, i.e. X-ray, sonography, bone scan, CT, MRI, and/or PET-CT.
- Single 12-lead ECGs will be obtained as outlined in the schedule of activities using an ECG machine that automatically calculates the heart rate and measures RR interval, QRS interval, QT interval, and QT interval corrected through use of Fridericia's formula (QTcF)/QT interval, PR duration.
- The occurrence and maximum grade of side effects observed throughout the study will be listed and tabulated according to type and dose level. Any AEs that the investigator reports as unrelated to the drug will also be reported. In this study, side effects will be assessed according to the NCI-CTCAE v5.0.
- Concomitant therapy (e.g. prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient will be collected in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to treatment discontinuation or end of study visit.

All assessments will be performed on the day of the specified visit unless a time window is specified (see Section 3.3.2).

Safety follow-up

All patients will be followed up for up to 28 days (+/- 3 days) after the last dose of the study treatment or discontinuation (regardless of the reason for discontinuation), in order to follow up toxicities and changes in concomitant medication.

Sample size and statistical methods:	**Primary analysis** The analysis will compare absolute changes for Ki67 expression between the baseline and the post-treatment tumor biopsy samples by central assessment. **Sample size** 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 in Dowsett M 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 (10.1214/aoms/1177728261). 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”). **Analysis methods** The primary analysis will be conducted on the modified intention to treat (mITT) set which includes all randomly assigned patients that accomplish major selection criteria and underwent the appropriate assessment for central Ki67 values. We will use Wilcoxon unpaired test set at 0.05 alpha level. It includes treatment as a factor. The response variable is the change in tumor cell proliferation as measured by Ki67 expression between baseline and the post-treatment tumor biopsy samples by central assessment. We propose declaring the superiority of giredestrant (GDC-9545) therapy if shown to be superior in this analysis. Supportive analysis for primary endpoint will be conducted in intention to treat set which includes all randomly assigned patients; and per protocol set which includes all randomly assigned patients without major protocol deviations. Missing values will be managed with last observation carried forward and multiple imputation methods for nonparametric and parametric methods, respectively. We will also analyze the primary endpoint with linear regression model adjusted by baseline Ki67 scores.

	Secondary endpoints will be analyzed in the mITT set, comprised by all randomly assigned patients that accomplish major selection criteria (Central Ki67 ≥ 10%) with Ki67 evaluable values at baseline and after the treatment. Subjects will be analyzed according to treatment allocated. The mITT set will be used for primary and secondary efficacy analysis with parametric and non-parametric tests. [redacted] The incidence and severity of AEs and safety parameters will be reported in safety analysis set. It includes all patients that received at least one dose of study drugs. We will summarize safety endpoints with frequencies and percentages per arm.
Study calendar:	Recruitment period: Estimated enrollment period will be 16 months. EoS will occur at 45 days (1.5 months) after last patient starts treatment unless premature termination of the study.

TABLE OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AI	Aromatase inhibitor
ALT	Alanine transaminase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
BC	Breast Cancer
BL	Basal-like
CAP	College of American Pathologists
CBR	Clinical benefit rate
CCCA	Complete cell cycle arrest
CDK4/6i	Cyclin-dependent kinase 4 and 6 inhibitors
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRF	Case report form
CSP	Clinical Study Protocol
CSPV	Clinical Safety and Pharmacovigilance
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal carcinoma in situ
DFS	Disease free survival
DoR	Duration of response
DSE	Drug Safety Evaluation
EBC	Early breast cancer
EC	Ethics committee

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EoS	End of study
EoT	End of treatment
ER	Estrogen receptor
ET	Endocrine therapy
FDA	Food and Drug Administration
FN	Febrile neutropenia
GCP	Good clinical practice
HIV	Human immunodeficiency virus
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone receptor, Hazard Ratio
IB	Investigator's Brochure (IB)
ICF	Informed consent form
HA	Alternative hypothesis
IDFS	Invasive disease-free survival
H0	Null hypothesis
IHC	Immunohistochemistry
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
IRB	Institutional review board
ITT	Intention-to-treat
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone-releasing hormone
mITT	Modified intention to treat
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events

NCI	National Cancer Institute
NET	Neoadjuvant endocrine therapy
NIS	National Inpatient Sample
NNT	Number needed to treat
OFS	Ovarian function suppresion
ORR	Objective response rate
OS	Overall survival
QD	Once a day
QoL	Quality of life
pCR	Pathologic complete response
PEPI	Preoperative endocrine prognostic index
PFS	Progression-free survival
PgR	Progesterone receptor
PO	Orally
PR	Partial Response
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
RR	Relative risk
SAE	Severe adverse effect
SERD	Selective estrogen receptor degrader
SERM	Selective estrogen receptor modulator
SmPC	Summary of product characteristics
SoC	Standard of care
TPC	Treatment of physician's choice
TtR	Time to response
UGT1A1	Uridine diphosphate-glucuronosyl transferase 1ª1

ULN	Upper limit of normal
WoO	Window of opportunity

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1 BACKGROUND ON HORMONE RECEPTOR-POSITIVE BREAST CANCER

1.1 Hormone receptor-positive breast cancer

Breast cancer (BC) is the most commonly diagnosed cancer worldwide, with an estimated global incidence of 2.3 million new cases and almost 685,000 deaths in 2020 (IACR 2020). Notably, whereas the incidence of postmenopausal BC has stabilized in many higher-income countries, the incidence among premenopausal women under the age of 40 is increasing (Heer et al., 2020).

Nearly 70% of all BC express the estrogen receptor (ER), which makes these tumors grow and progress in response to this hormone. Over the last decade, molecular characterization allowed the identification of Luminal A and Luminal B as the main molecular subtypes of ER-positive BC (TGCA 2012; Prat et al., 2013). Although it is not clear the difference between the two subtypes regarding endocrine therapy sensitivity (Dunbier et al., 2011; Ellis et al., 2011), Luminal A tumors present a better prognosis at 5 to 10-year follow-up compared to the Luminal B subtype (TGCA 2012; (Prat et al., 2016).

1.2 Treatment of hormone receptor-positive early breast cancer

Endocrine therapy (ET) is regarded the mainstay for ER-positive/HER2-negative BC and should be considered for all patients with ER-positive early BC (EBC).

In 1897, ovarian function suppression (OFS) was the first systemic therapy for cancer. In the 1960s, ET by modulation of estrogen activity and/or synthesis appeared as key target for the treatment of ER-positive BC. In the 1970s, tamoxifen, a non-steroidal selective estrogen-receptor modulator (SERM), was approved by the Food and Drug Administration (FDA) as one of the first developed oral ET for women with ER-positive BC. Subsequently, aromatase inhibitors (AIs), which block the conversion of androgens into estrogens, were developed and commercialized.

Currently, ET for EBC includes tamoxifen and aromatase inhibitors (AIs) with or without OFS. Despite the effectiveness of available therapies, many patients ultimately experience disease relapse or develop resistance to these agents (Angus et al., 2017). According to ESMO Clinical Practice Guidelines, all luminal-like tumors should be treated with ET. Addition of chemotherapy will depend on the amount of disease burden, individual risk of recurrence, presumed responsiveness to ET and patient preferences.

Tamoxifen is the current adjuvant standard of care (SoC) for premenopausal patients with low-risk (stages I-IIA and luminal A tumors) ER-positive EBC, where treatment duration is usually for 5 to 10 years (Cardoso et al., 2019). Notably, 5 years of tamoxifen reduces their risk of death from breast cancer at 15 years by about one third (Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al., 2011).

AIs for 5 years have demonstrated superiority over tamoxifen both in the advanced and early settings in postmenopausal patients. Compared to tamoxifen, AIs produce proportional reductions

in recurrence rates of about 30%. In premenopausal women, AIs are also considered in high-risk patients in combination with effective OFS (Breast International Group (BIG) 1-98 Collaborative Group et al., 2005; Howell et al., 2005).

In the SOFT and TEXT trials, AI plus OFS was compared to tamoxifen plus OFS in premenopausal women. In a combined updated analysis of these trials, at 12 and 13 years of median follow-up, a statistically significant 17% reduction of distant metastasis was observed, favoring AI with OFS (P = 0.03). However, overall survival did not significantly differ between the two clinical trials (Francis, 2019; Francis et al., 2015). A recent meta-analysis comparing AI plus OFS or tamoxifen treatment in premenopausal women shows that AI plus OFS reduces the risk of breast cancer recurrence rather than tamoxifen, especially in patients with high-risk, without breast cancer mortality reduction (Bradley et al., 2022). In addition, for patients with high-risk node-positive EBC, the addition of the cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) abemaciclib to ET for 2 years in the adjuvant setting significantly improved invasive disease-free survival (IDFS) of patients (Johnston et al., 2020).

However, these treatments are associated with short- and long-term side effects that determine the discontinuation of treatment. Class side-effects of AIs are musculoskeletal symptoms, osteoporosis and bone fractures (Bradley et al., 2022; Breast International Group (BIG) 1-98 Collaborative Group et al., 2005; Ea, 2007; Howell et al., 2005) while those of tamoxifen are thromboembolic disease and endometrial cancer (Fisher et al., 1998). OFS worsens tolerance and side effects to adjuvant ET due to induced early menopause. On the other hand, abemaciclib has been associated with diarrhea, fatigue, neutropenia, leucopenia, and nausea (Rugo et al., 2021).

In 2002, fulvestrant became the first-generation selective estrogen-receptor degraders (SERDs) to be used in advanced and metastatic BC (Osborne et al., 2002). SERDs have the potential to completely downregulate estrogen signaling by binding to, blocking and degrading Ers. In EBC, fulvestrant research was limited by the modest benefits over AI in advanced BC. However, preoperative studies provided consistent superiority in inhibition of the cell proliferation, defined by Ki67 marker, over tamoxifen in premenopausal patients (Dowsett, Nicholson, et al., 2005; Young et al., 2008).

1.3 Neoadjuvant endocrine treatment for ER-positive BC

In EBC, neoadjuvant therapy has become one of the preferred treatment options. Its efficacy has been proven to be equivalent to adjuvant therapy, with some advantages such as the improvement of surgical resection and providing prognostic information. Whereas pathologic complete response (pCR) is associated with longer progression-free survival (PFS) and OS in the case of triple- negative and HER2- positive tumors, it is not a good prognostic biomarker in luminal breast cancer (Cortazar et al., 2014; Spring et al., 2020).

Some clinical trials have compared the benefit of neoadjuvant endocrine therapy (NET) versus four cycles of neoadjuvant chemotherapy in luminal breast cancer (Alba et al., 2012; Semiglazov et al., 2007). Semiglazov et al. shown that postmenopausal patients with ER-positive tumors treated with either NET (aromatase inhibitors) or chemotherapy had the same rate of overall objective response. In contrast, the GEICAM/2006-03 trial reported superior clinical benefit rates of neoadjuvant chemotherapy over NET in premenopausal and postmenopausal patients with ER-positive BC, especially in patients with a high proliferation rate (Ki67 > 10%). Nevertheless, a similar clinical response was observed between treatments in patients with a low proliferation rate (Ki67 < 10%), thereby suggesting that this group of patients could avoid chemotherapy in the adjuvant setting. To further support these data, a meta-analysis of prospective randomized clinical trials with at least one arm of NET (either monotherapy or dual therapy) shown similar response rates with NET than neoadjuvant chemotherapy but with substantially less toxicity (Spring et al., 2016).

NET is mainly used in patients in the preoperative treatment of ER-positive/HER2-negative BC who are eligible for neoadjuvant treatment but not for chemotherapy (Colomer et al., 2019). In postmenopausal women, NET with an AI (such as anastrozole, letrozole, or exemestane) is more effective than tamoxifen (Cataliotti et al., 2006; Eiermann et al., 2001; Ellis et al., 2011; Ellis & Ma, 2007). Although 3 (Cataliotti et al., 2006)and 4 (Eiermann et al., 2001; Ellis & Ma, 2007) months has been the standard treatment duration of NET, there is consensus that this length of treatment is insufficient to reach maximal tumor response. Non-randomized studies suggest that some tumors benefit from a longer duration (6-12 months) of NET (Carpenter et al., 2014; Llombart-Cussac et al., 2012; Spring et al., 2016).

1.4 Rationale for Ki67 biomarker as primary endpoint

There has been a huge effort to find surrogate markers that can select a good prognosis population in patients treated with NET. Because anti-estrogen therapy mainly induces cell-cycle arrest, markers of tumor cell proliferation have been used to measure the *in situ* action of these drugs. In this scenario, Ki67 has emerged as a biomarker of efficacy after neoadjuvant treatment of luminal breast cancer. Ki67 is a nuclear antigen expressed by all proliferating cells between the late G1 and M phases of the cell cycle (Scholzen & Gerdes, 2000). There are three main studies showing that a lower Ki67 score in response to NET results in better long-term disease-free recurrence outcomes, while high Ki67 levels predicts worse prognosis (Guerrero-Zotano & Arteaga, 2017).

The IMPACT trial demonstrated that 2 and 12 weeks of neoadjuvant treatment with anastrozole significantly decreases Ki67 expression (76% and 82%, respectively) compared to tamoxifen alone (59% and 62%, respectively) or the combination of anastrozole plus tamoxifen (64% and 61%, respectively), and was correlated with an increased recurrence-free survival. However, there were no significant differences in overall response. (Dowsett, Smith, et al., 2005; I. E. Smith et al., 2005).

In the P024 study, 16 weeks of neoadjuvant treatment with letrozole achieved a greater overall response rate (ORR) compared to tamoxifen (55% vs. 36%, respectively) and a significant reduction of Ki67 (87% vs. 75%, respectively) (Ellis & Ma, 2007).

The ACOSOG Z1031 trial compared the efficacy of neoadjuvant exemestane, letrozole or anastrozole treatment for 16 to 18 weeks and shown that all three AIs produced an equivalent rate of Ki67 suppression, preoperative endocrine prognostic index (PEPI) score and there were no differences in surgical outcome (Ellis et al., 2011).

The shorter 2-4 weeks period of NET has become a window of opportunity (WoO) for molecular-based studies to provide early biological signals that may guide development in early and advanced settings. Notably, POETIC study was a phase III study showing that two weeks of neoadjuvant AI followed by standard adjuvant therapy was a safe treatment option and improved outcome in postmenopausal women with ER-positive EBC. The measurement of Ki67 levels at baseline and at 2 weeks treatment demonstrated that patients with low Ki67 levels (<10%) had a lower risk of recurrence than patients with high Ki67 levels (>10%) (I. Smith et al., 2020).

In this line, the phase II NEWEST trials helped establish the optimal dose of fulvestrant 500 versus 250 after 4 weeks of treatment on the bases of Ki67 levels and showed that 500mg dose achieved greater suppression of cell proliferation (Kuter et al., 2012).

Table 1 summarizes clinical trials with NET for the treatment of postmenopausal women with ER-positive BC and its impact to decrease Ki67 marker.

Table 1. Clinical trials with neoadjuvant endocrine therapy in ER-positive BC.

Clinical Trial	Phase	Study	% Ki67 decrease
N/A	II	Neoadjuvant treatment of postmenopausal BC with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, tamoxifen, or Combined with tamoxifen (IMPACT) multicenter double-blind randomized trial	After 2 and 12 weeks with anastrozole (76% and 82%, respectively), tamoxifen (59% and 62%, respectively), or combination treatment (64% and 61%, respectively).
N/A	III	Preoperative treatment of postmenopausal BC patients with letrozole: A randomized double-blind multicenter study (P024 trial)	After 16 weeks with letrozole or tamoxifen (87% vs. 75%, respectively).
NCT00265759	III	A Randomized Phase III Trial Comparing 16 to 18 Weeks of Neoadjuvant Exemestane (25 mg Daily), Letrozole (2.5 mg), or	After 16-18 weeks with exemestane, letrozole or

		Anastrozole (1 mg) in Postmenopausal Women With Clinical Stage II and III Estrogen Receptor Positive Breast Cancer (ACOSOG Z1031 trial)	anastrozole (81,2%, 87,1% and 78%, respectively).
NCT02338310	III	Trial of Perioperative Endocrine Therapy – Individualising Care (POETIC trial)	After 2 weeks with anastrozole (75%).
NCT00093002	II	A Randomized, Open-Label, Multicenter, Phase II Study Comparing the Effects on Proliferation and the Efficacy and Tolerability of Fulvestrant (FASLODEX®) 500 mg With Fulvestrant (FASLODEX®) 250 mg When Given as Neoadjuvant Treatment in Postmenopausal Women With Estrogen Receptor Positive Breast Cancer (T2, 3, 4b, N0-3, M0) (NEWEST trial)	After 4 weeks with 500mg or 250mg of fulvestrant (78.8% vs 47.4%, respectively).

N/A: not applicable.

1.5 Investigational agent : giredestrant (GDC-9545)

Giredestrant (GDC-9545) is a novel highly potent, orally available, second-generation SERD that is currently being developed for the treatment of patients with ER-positive BC. It binds with nanomolar affinity to both wild-type and mutant ESR1^{Y537S} ER, encoded by the *ESR1* gene, and decrease their protein levels by inducing their proteasome-mediated degradation, which greatly reduces the ER signaling pathway (Jhaveri et al., 2021; Liang et al., 2021).

Giredestrant (GDC-9545) potently inhibits cell proliferation *in vitro* and exhibits a dose-dependent anti-tumor activity in several murine models, including cell lines and patients derived xenografts. In addition, it has shown excellent *in vitro* and *in vivo* safety and pharmacokinetic profiles. Notably, the effective doses ranged from 0.1 to 10mg/kg/day and were all well tolerated (Liang et al., 2021).

1.5.1 Clinical overview of giredestrant (GDC-9545)

The study NCT03916744 was a phase I, open-label, multicenter trial of giredestrant (GDC-9545) to evaluate pharmacodynamics, pharmacokinetics, safety, and biologic activity of the drug in postmenopausal women with stage I-III operable ER-positive/HER2-negative untreated BC. 75 patients were assigned to 15 (±2) days of treatment with giredestrant (GDC-9545) orally once daily (PO QD) at a dose of either 10, 30, or 100 mg followed by surgery. Tumor tissue samples were collected at baseline and at the end of treatment. The primary objective of the study was to measure changes in the Ki67 between pre- and post-treatment samples. Preliminary results from 47 evaluated patients shown that 77% were classified as Luminal A and 23% Luminal B at baseline. Giredestrant (GDC-9545) treatment was well tolerated, no grade 4 or 5 adverse events (AEs) were reported and single serious grade 3 that appeared were unrelated to giredestrant (GDC-9545). In addition, it was biologically active at all doses. The post-treatment Ki67 reduction was 80% at 10 mg, 76% at 30mg and 80% at 100mg. Notably, 51% of tumors exhibited complete

cell cycle arrest (CCCA, Ki67 ≤2.7%) and the mean post-treatment proportional reductions of ER and PgR (progesterone receptor) H-scores were 71% (95% CI: 67–75) and 60% (95% CI: 51–70), respectively (Moore et al., 2021).

The phase II coopERA trial (NCT04436744) was a two arm, open-label, multicenter trial aimed at evaluating the efficacy, safety and pharmacokinetics of giredestrant (GDC-9545) plus palbociclib compared with anastrozole plus palbociclib in postmenopausal women with untreated ER-positive/HER2-negative EBC. 221 patients with baseline Ki67 score ≥5% were randomized 1:1 to receive 14 days of anastrozole (1 mg, PO QD) or giredestrant (GDC-9545) (30 mg, PO QD) (window-of-opportunity phase, WoO) followed by 16 weeks (four 28-days cycles) of additional neoadjuvant palbociclib (125 mg, PO, D1-21) treatment prior to surgery. The primary objective of the study was to measure tumoral Ki67 changed between baseline and post-WoO samples. In ESMO Breast 2021, preliminary results were shown for 83/202 planned patients. Two-week relative Ki67 reduction was significantly greater with giredestrant (GDC-9545) than anastrozole (80% versus 67%, respectively) and a consistent Ki67 suppression was observed in patients with baseline Ki67 ≥20% (giredestrant (GDC-9545): 83% reduction; anastrozole: 71%) or <20% (65% vs 24%). After 14 days of treatment, 25% of tumors exhibited complete cell cycle arrest (secondary objective) with giredestrant (GDC-9545) versus 5% with anastrozole. Patients treated with giredestrant (GDC-9545) had fewer AEs than anastrozole.

Table 2 summarizes ongoing clinical trials with giredestrant (GDC-9545) for the treatment of early or advanced hormonal receptor-positive BC. In addition, giredestrant (GDC-9545) is also being studied in the treatment of ER-positive/HER2-positive BC.

Table 2. Ongoing clinical trials with giredestrant (GDC-9545) in BC.

Clinical Trial	Phase	Study
NCT03916744	I	A Phase I, Multicenter, Open-Label Preoperative, Short-Term Window Study of GDC-9545 in Postmenopausal Women With Stage I-III Operable, Estrogen Receptor-Positive Breast Cancer
NCT03332797	Ib/II	Multicenter, Open-Label, Dose Escalation, Dose Expansion Study Evaluating the Safety, Pharmacokinetics, and Activity of GDC-9545 Alone or in Combination With Palbociclib and/or LHRH Agonist in Patients With Locally Advanced or Metastatic Estrogen Receptor-Positive Breast Cancer
NCT04802759	Ib/II	Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Patients With Breast Cancer (MORPHEUS-Breast Cancer)

NCT04436744	II	A Randomized, Multicenter, Open-Label, Two-Arm, Phase II, Neoadjuvant Study Evaluating the Efficacy, Safety, and Pharmacokinetics of GDC-9545 Plus Palbociclib Compared With Anastrozole Plus Palbociclib for Postmenopausal Women With Estrogen Receptor-Positive and HER2-Negative Untreated Early Breast Cancer (coopERA trial)
NCT04576455	II	Randomized, Open-Label, Multicenter Study Evaluating the Efficacy and Safety of GDC-9545 Compared With Physician's Choice of Endocrine Monotherapy in Patients With Previously Treated Estrogen Receptor-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer (acelERA trial)
NCT04961996	III	Randomized, Open-Label, Multicenter Study Evaluating the Efficacy and Safety of Adjuvant giredestrant Compared With Physician's Choice of Adjuvant Endocrine Monotherapy in Patients With Estrogen Receptor-Positive, HER2-Negative Early Breast Cancer (lidERA trial)
NCT05306340	III	Randomized, Open-Label, Multicenter Study Evaluating the Efficacy and Safety of giredestrant Plus Everolimus Compared With Exemestane Plus Everolimus in Patients With Estrogen Receptor-Positive, HER2-Negative, Locally Advanced or Metastatic Breast Cancer (evERA trial)
NCT05296798	III	Randomized, Open-Label Study Evaluating the Efficacy and Safety of giredestrant in Combination With Phesgo Versus Phesgo After Induction Therapy With Phesgo + Taxane in Patients With Previously Untreated HER2-Positive, Estrogen Receptor-Positive Locally-Advanced or Metastatic Breast Cancer (heredERA trial)
NCT04546009	III	Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of GDC-9545 Combined With Palbociclib Compared With Letrozole Combined With Palbociclib in Patients With Estrogen Receptor-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer (persevERA trial)

1.6 Rationale for developing a Window-of-Opportunity study in premenopausal patients with ER-positive/HER2-negative EBC

The reduction of Ki67 levels after NET has been shown to be a good marker of decreased tumor proliferation in postmenopausal patients (refer to Table 1). Although NET has also been studied in premenopausal patients with EBC, little is known about its impact on Ki67 marker. The NEST

clinical trial aimed at comparing the efficacy of NET versus neoadjuvant chemotherapy for 24 weeks in premenopausal South Corean patients with ER-positive, HER2-negative, lymph node positive breast cancer. While better clinical responses were observed in patients receiving neoadjuvant chemotherapy, there were no differences in the Ki67 marker between the two treatment regimens (Kim et al., 2020).

The WoO EMPRESS study aims at evaluating the changes in the Ki67 proliferation biomarker between baseline and post-treatment tumor samples of premenopausal ER-positive/HER2-negative EBC patients (with centrally confirmed Ki67 ≥10%) treated for 15 days with either single agent giredestrant (GDC-9545) or tamoxifen.

Strategically, the EMPRESS study aims to provide evidence on the biological superiority of giredestrant (GDC-9545) over tamoxifen in premenopausal EBC patients. Notably, a positive result may justify the development of future studies with giredestrant (GDC-9545) without OFS in this population. In addition, while a direct comparison of giredestrant (GDC-9545) treatment to a regimen combined with OFS in premenopausal women is not feasible due to the short period of treatment, an indirect comparison on Ki67 decrease at 15-days treatment could shed light as to whether giredestrant (GDC-9545) has the potential to decrease tumor cell proliferation in this patient population, in line with the results seen in postmenopausal patients treated with giredestrant (GDC-9545) (NCT03916744), letrozole (own series), and letrozole plus palbociclib (NCT03819010).

2 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are described in the **Table 3.**

Table 3. Summary of objectives and endpoints of EMPRESS trial.

PRIMARY OBJECTIVES	**PRIMARY ENDPOINT**
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: giredestrant vs Arm B: tamoxifen).	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: giredestrant vs Arm B: tamoxifen).
SECONDARY OBJECTIVES	**SECONDARY ENDPOINTS**
• To measure complete cell cycle arrest (CCCA) in all arms, defined by Ki67≤2.7% in post-treatment samples.	• CCCA in all arms, defined as the percentage of participants with centrally assessed Ki67 scores ≤2.7% stained nuclei upon treatment (post-treatment samples).
• To analyze changes in ER and PgR levels, and molecular profiling using HTG.	• Changes in markers (such as ER and PgR levels) and molecular profiling using HTG (PAM-like molecular test).
• To evaluate toxicity according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5.0.	• Incidence and severity of adverse events (AEs), with severity determined in accordance to NCI-CTCAE v.5.0. *Note: Patient safety and AEs will be evaluated using the NCI-CTCAE v.5.0. All AEs and serious adverse events (SAEs) will be assessed to determine the safety and tolerability of the treatment.*
[redacted]	[redacted]
[redacted]	[redacted]

**Post-treatment sample should be collected after treatment, either on Day 15 or Day 15 + 1. If fresh post-treatment biopsy cannot be obtained within + 1 day from last day of treatment (that is on D15 or D15 +1), treatment will be extended to 16 days and post-treatment analyses will be done in surgery/biopsy sample obtained on the following day (be it D15 + 2 days).*

3 STUDY OVERVIEW

3.1 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 summarizes the EMPRESS study design.

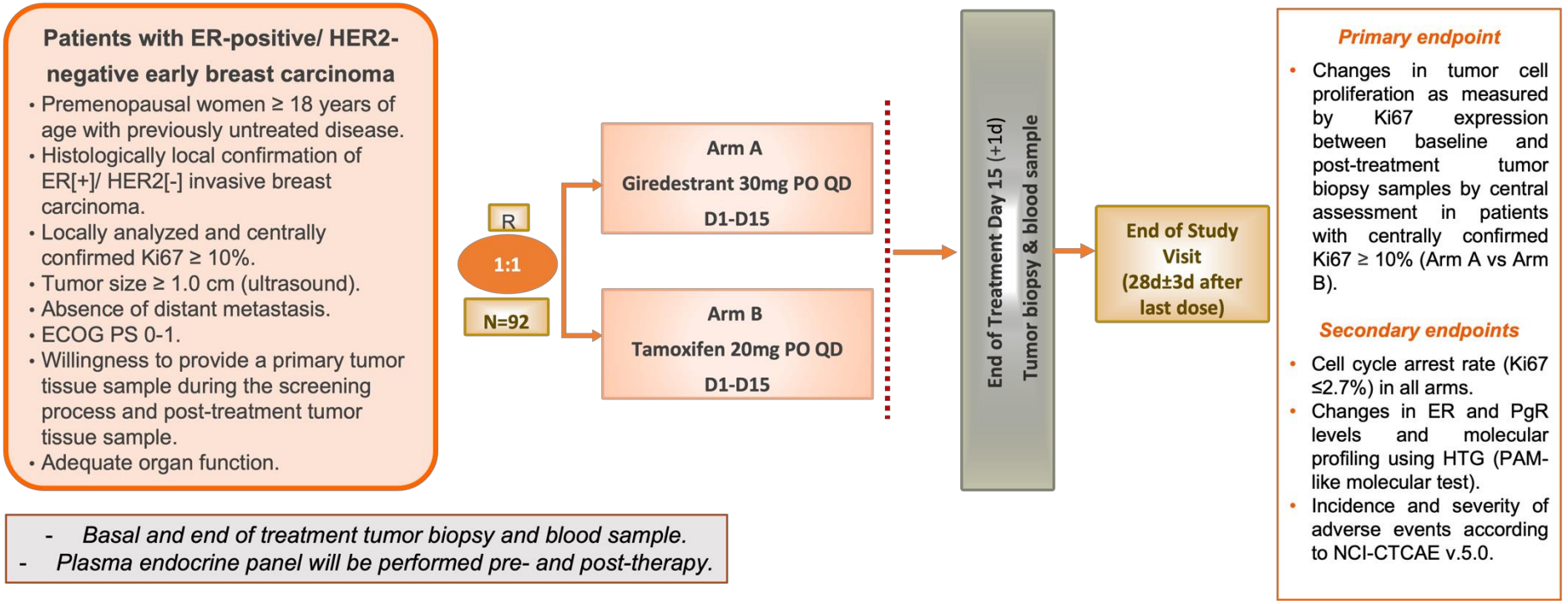

Figure 1. EMPRESS study design. Abbreviations: **d**: days; **ER**: Estrogen receptor**; PgR**: Progesterone receptor; **PO**: orally; **QD**: daily; **R**: randomization.

3.2 Study treatment management

Eligible patients will be randomly assigned in a 1:1 ratio to either experimental Arm A (treatment with giredestrant (GDC-9545)) or control Arm B (treatment with tamoxifen). During the study treatment (a total of 15 days*), patients will receive either giredestrant (GDC-9545) 30 mg PO QD or tamoxifen 20 mg PO QD, both as a single agent.

- Arm A: giredestrant (GDC-9545): 30mg, PO, QD, on days 1-15.
- Arm B: tamoxifen: 20mg, PO, QD, on days 1-15.

Giredestrant and tamoxifen can be taken with or without food at approximately the same time each day as per study treatment regimen.

Patients will be treated for a total of 15 days and treatment will last until any of the situations described in **Section 3.3.3.**

Dose delays and guidelines of management of the patients who experience adverse events associated with the study drugs are outlined in **Section 7.**

**Note: if post-treatment surgery or biopsy cannot be performed within + 1 day from last day of treatment (that is, on D15 or D15+1), 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).*

3.3 Study schedule summary

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).

3.3.1 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; procedures to be performed are described in **Appendix *1*: Schedule of study assessments and procedures**.

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.

3.3.2 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. Refer to **Section 7** for more information regarding toxicities.

3.3.3 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.

3.3.4 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).

4 PATIENT SELECTION

Patient eligibility will be reviewed and documented by a suitable member of the investigator's study team before the patients are enrolled in the study. This study can fulfil its objectives only if appropriate patients are enrolled. Patients must meet ALL the selection criteria. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1 Target Study Population

This study will enroll female patients ≥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 (reference lesion). Patients with distant metastatic disease are not allowed.

Well-define premenopausal status refers to women who have not reached the postmenopausal state because they are not permanently infertile due to prior bilateral oophorectomy, age ≥60 years or age <60 years with amenorrhea for ≥12 months and estradiol and FSH levels in the postmenopausal range.

Patients diagnosed with multifocal or multicentric breast cancer with at least one tumor lesion ≥1.0 cm in the longest diameter by ultrasound (reference lesion) will be eligible for the study only if the two largest lesions have been histologically confirmed in the clinical evaluation and meet the pathologic criteria for ER positivity and HER2 negativity. The reference lesion will be used to assess changes in the tumor cell proliferation as measured by Ki67 expression.

Patients must present an adequate organ function. Patients must agree to provide a primary tumor tissue sample and a blood sample during the diagnostic process (if the patient had a biopsy sample taken no longer than 8 weeks prior to initiation of study treatment, it can be used as baseline) and post-treatment tumor tissue and a blood sample (breast biopsy or breast surgery).

**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.*

4.2 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 10^9/L (1500/mL), platelet count ≥ 100.0 x10^9/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.

4.3 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.

5 STUDY DRUG INFORMATION

The investigational medicinal products (IMPs) for this study are giredestrant (GDC-9545) and tamoxifen.

Complete description of the IMP will be documented in its respective Investigator Brochure (IB) and summary of product characteristics (SmPC), located in the Site/Investigator's file. Summarized information is reported in this section.

5.1 Formulation, packaging, and handling

Giredestrant (GDC-9545) will be supplied by the Sponsor as 30 mg capsules of GDC-9545 (free base equivalent), packaged in high-density polyethylene bottles with a plastic child-resistant cap with induction seal and desiccant. For information on the formulation of giredestrant (GDC-9545), see giredestrant's (GDC-9545) IB.

Tamoxifen will be supplied by each investigational site as 20 mg film-coated tablets. For information on the formulation of tamoxifen, see the SmPC local prescribing information.

All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Refer to the giredestrant's (GDC-9545) IB and the tamoxifen's SmPC local prescribing information for more information on IMP handling, including preparation and storage, and accountability.

5.2 Dosage, administration, and compliance

During the treatment phase, starting with Day 1, patients will be given the first dose of study treatment, which will be either giredestrant (GDC-9545) 30 mg (Arm A) or tamoxifen 20 mg (Arm B) in the clinic after the study assessments. Then, patients will be instructed how to take giredestrant (GDC-9545) or tamoxifen orally, daily at their homes during the following 14 days D2 to D15 (to finalize a total of 15 days of treatment).

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

Giredestrant (GDC-9545) 30 mg PO QD and tamoxifen 20 mg PO QD should be taken orally with food at approximately the same time each day as per study treatment regimen. The capsule or tablet should be swallowed whole and should not be chewed, crushed, or opened. If a dose is missed, the dose should be made up unless the next dose is due within 6 hours (vomited doses should not be made up).

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. Patients will be instructed to bring all unused study medication and their medication diaries to the clinic at specified study visits (see schedule of assessments and activities).

Compliance will be assessed by investigator site team staff (e.g. by counting returned capsules/tablets, clinic visit patient interview notes and reviewing patient diaries).

Details on treatment administration should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication errors, drug abuse or misuse, along with any associated adverse events should be reported in the eCRF.

5.3 Study drug storage and drug accountability

The IMP giredestrant will be provided by the Sponsor. The IMP tamoxifen will be provided by each investigational site.

The Investigator and other authorized personnel [e.g., pharmacist]) are responsible for safe and proper handling and storage of the study drug at the investigational site, for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol. Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff. Investigators and site staff are reminded to continuously monitor room storage temperatures and ensure that thermometers are working correctly as required for proper storage of investigational products. These may include thermometers for both the room and refrigerator storage. Any temperature excursions must be reported immediately to the Sponsor and documented. Once a deviation is identified, the IMP must be quarantined and not used until the Sponsor provides documentation of permission. Refer to the pharmacy manual and/or the giredestrant IB and the tamoxifen local prescribing information for information on IMP handling, including preparation and storage, and accountability.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using an Interactive Response Technology Platform to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs.

At the end of the trial, the Sponsor will provide instructions as to disposition of any unused IMP. If the Sponsor authorizes destruction at the trial site, the Investigator must ensure that the

materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor.

The investigational site must obtain written authorization from the Sponsor before any IMP is destroyed, and the destruction must be adequately documented.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

The investigational sites will be supplied with study drug according to the sites' needs. The investigational site will acknowledge receipt of IMP and confirm the shipment condition and contents. Any damaged shipments will be replaced. IMPs must be stored according to their IB and/or local prescribing information.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

5.4 Treatment compliance

In the first visit D1, patients will be given the first dose of treatment and will be instructed how to take giredestrant (GDC-9545) or tamoxifen orally, daily at their homes during the following 14 days D2 to D15 (to finalize a total of 15 days of treatment*). At the study visits, the medication diary as well as unused tablets or capsules and all containers or packaging (used or unused) of study treatment should be collected and reviewed for drug accountability.

Treatment compliance will be defined as the number of capsules or tablets taken divided by the expected number of capsules or tablets and reported as a percentage. Capsules or tablets that are not returned will be considered to have been taken, unless otherwise specified in the patient's diary and/or eCRF. Note that dosing eCRFs should be completed using the following prioritization: 1) site pharmacy drug accountability logs (IMP disbursed minus IMP returned), 2) clinic visit patient interview notes, and 3) patient daily dosing diary.

^Note: If post-treatment surgery or biopsy cannot be performed within + 1 day from last day of treatment (that is, D15 or D15+1), treatment will be extended to 16 days and surgery or biopsy will be performed on the following day (be it D15 + 2 days). This will be scheduled in advanced and determined with the investigator to ensure availability of patient.

5.5 Treatment modifications and discontinuation

Safety and tolerability of all patients will be closely monitored throughout study treatment and the follow-up period using the US NCI-CTCAE version 5.0. Patients will be assessed in order to detect any side effects before administering new study treatment. Treatment will only be administered if clinical evaluation and local laboratory test results are acceptable.

Patients whose treatment is interrupted or permanently discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first, which includes all study assessments appropriate to monitor the event.

Treatment administration may be delayed assessing or treating AEs.

Interruptions or delays due to any other reason should be discussed with the Medical Monitor.

No dose modification will be permitted for giredestrant (GDC-9545) or tamoxifen. See **Table 5. Guidelines for Management of Patients Who Experience Adverse Events Associated with Giredestrant (GDC-9545).** In Section 7 for further details on management of AEs.

Study treatment may be temporarily suspended in patients who experience toxicity considered related to study drug.

5.6 Medication errors and overdose

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. Cases of overdose, along with any associated AEs, should be reported as described in Section 7.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until resolution.
3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).

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

5.7 General concomitant medication and additional assistance guidelines

Concomitant treatment and prior medication are defined as non-investigational medicinal product (non-IMP). Concomitant treatment includes any prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to treatment discontinuation or end of study visit.

Information on concomitant medication will include start date, end date, brand or generic name, route of administration, dose, and treatment indication. The following **concomitant treatments** are permitted during the study:

- Symptomatic anti-emetics and anti-diarrheal therapy may be administered at the investigator's discretion.
- Bone-sparing agents (e.g., bisphosphonates, denosumab for the treatment of osteoporosis/osteopenia) are allowed in the study provided patients are on stable doses for at least 4 weeks prior to randomization.
- Patients can be treated per standard of care except for use of any prohibited therapies.

All concomitant medication and/or therapies should be documented in the patient's eCRF.

Cautionary therapies may include:

- ***Medications* Associated *with Bradycardia***

Investigators should use medical judgment and exercise caution when considering initiation of concomitant medication known to cause decreases in heart rate including, but not limited to, β-blockers and calcium channel antagonists. An alternative therapy should be used when possible.

Patients on a stable dose of a β-blocker or calcium channel antagonist for preexisting baseline conditions (e.g., hypertension) should be monitored closely in case dose modification is warranted.

- **Herbal Therapies**

Herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator and must be reported as concomitant therapy in the eCRF.

Any medications deemed necessary to ensure patient safety and well-being may be administered at the discretion of the investigator with the exception of prohibited therapies contained in **Section 5.8.**

5.8 Prohibited therapies and medication

Use of the following concomitant therapies is prohibited during study treatment as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited during study treatment.
- Any concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, biologic therapy, or radiotherapy) is prohibited until after the end of study visit.
- Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate, oral contraception, hormone-eluting intrauterine devices, Gonadotropin-releasing hormone (GnRH) agonists and selective ER modulators (e.g., raloxifene) are prohibited until after the end of study visit.

- Treatment with strong CYP3A4 inhibitors or inducers within 14 days or 5 drug elimination half-lives (whichever is longer) prior to randomization. *Note: this includes consumption of grapefruit, grapefruit juice, grapefruit supplements, or Seville oranges (potent CYP3A inhibitors) within 3 days prior to randomization.*
- Potent inhibitors of CYP2D6 (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion).

The investigator should consult the prescribing information in giredestrant's (GDC-9545) IB and tamoxifen's SmPC for information on prohibited therapies and recommended dose adjustments for concomitant medications. Giredestrant DDI study (GP44001) suggests that giredestrant is a moderately sensitive CYP3A substrate. It is advised that investigators consider alternatives to the concomitant use of moderate CYP3A inducers with giredestrant or giredestrant combination treatment. If this is not possible or there are no suitable alternatives, co-administration with moderate CYP3A inducers should be generally limited to short term use (approximately 30 days). Concomitant medications that inhibit CYP2D6 may lead to reduced concentrations of the active tamoxifen metabolite endoxifen. Therefore, potent inhibitors of CYP2D6 (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided during tamoxifen treatment. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take tamoxifen.

In addition, the investigator should contact the study Medical Monitor if questions arise regarding medications not listed above. Enrolled patients who subsequently require the use of any prohibited therapies must be discontinued from study treatment.

5.8.1 Interaction with other drugs

Interaction of giredestrant (GDC-9545) with other medicinal products and other forms of interaction

Giredestrant is a moderately sensitive CYP3A substrate. Co-administration giredestrant with the strong CYP3A inhibitors and inducers should be avoided. Refer to the giredestrant's (GDC-9545) IB for a complete summary of safety information and DDIs.

Interaction of tamoxifen with other medicinal products and other forms of interaction

When tamoxifen is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such co-administration is initiated, careful monitoring of the patient is recommended.

As tamoxifen is metabolized by cytochrome P450 3A4, care is required when co-administering with drugs, such as rifampicin, known to induce this enzyme as tamoxifen levels may be reduced. The clinical relevance of this reduction is unknown. Therefore, is recommended to avoid the coadministration of tamoxifen and CYP3A inhibitors/inducers.

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a 65-75% reduction in plasma levels of one of the more active forms of the drug, i.e., endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants (e.g. paroxetine) in some studies.

As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided.

6 ASSESSMENTS AND STUDY PROCEDURES

6.1 Patient entry procedures

6.1.1 Informed consent

Written informed consent from the patient (or the patient's legally authorized representative) must be signed and dated before her participation in the study and before performing any study specific procedure. Patients will be informed as to the nature of the study drug and will receive pertinent written information regarding the study objectives, possible benefits, and potential AEs. They will also receive information on the follow-up procedures and possible risks they will be exposed to. The informed consent form will also inform patients about how biological samples will be obtained and collected and its legal implications. A copy of the signed ICF must be provided to the patient or the patient's legally authorized representative. Patients have the right to voluntarily withdraw from the study at any time for any reason, and this will not affect any future medical treatment the patient will receive.

6.1.2 Patient allocation

The following steps must be taken before registering patients to this study:

1. Completion of patient eligibility checklist by the investigational site, once checked all selection criteria. For patients with locally determined basal Ki67 between 10% and 19%, after receiving central Ki67 score result.

   Note for Ki67 selection criteria: Ki67 will be analyzed locally at the time of inclusion. For patients with basal Ki67 ≥20% according to local analysis, Ki67 ≥10% will be centrally confirmed retrospectively after inclusion. For patients with basal Ki67 levels between 10% and 19% according to local analysis, Ki67 ≥10% will need to be centrally confirmed before inclusion.

2. Registration of patient in the Sponsor's study database.

3. Randomization using Sponsor's study database.

Confirmation of patient allocation using Sponsor study database:

Each patient will be identified with a unique patient number (UPN) for this study obtained from eCRF. All data will be recorded with this identification number on the appropriate eCRFs.

Confirmation of patient's eligibility for study participation will be recorded on the eCRF by the investigational site and verified by the study medical monitor prior to inclusion (all screening data needs to be completed 48h prior to randomization to allow enough time for medical monitor review). The investigator is responsible for safeguarding patient information (i.e., age, name, address, telephone number, social security number, and study identification number), ensuring access to this information by Health Authorities if necessary. These records will remain confidential for the period of time stipulated by current legislation.

Randomization

Premenopausal women with ER[+]/HER2[-] and Ki6 ≥10% early breast cancer will be randomized in a 1:1 ratio to giredestrant (GDC-9545) or tamoxifen arms.

Randomization will be accomplished using an automated web randomization system (eCRF provided by the Sponsor). The system contains the randomization schedule. At the screening visit, the investigative site will obtain the patient number from the eCRF and will contact randomization system (online). The site will enroll the patient by indicating minimal information sufficient to distinguish one patient from another and receive the patient identity (ID) number. At the baseline visit, the system will associate that patient with the next available treatment on the randomization schedule and provide the randomization number.

Refer to the separate study manual for instructions for study entry, patient ID assignments, and randomization procedures.

6.2 Visit schedule

After confirming eligibility through the screening process as indicated above, patients will be scheduled for baseline visit at day 1 (D1) of treatment within 48 h after randomization.

All screening tests and evaluations must be completed within the protocol scheduled time windows and reviewed to confirm that patients meet all eligibility criteria within 28 days prior to the first administration of study medication (dosing). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

The study will consist of a screening period of up to 28-day, a window-of-opportunity 15-day treatment phase, an EoT visit (+ 1 day) and an EoS visit (28 days +/- 3 days after the final dose of study treatment). 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 surgery or biopsy may be performed on the following day (be it D15 + 2 days).

Assessments scheduled for day 1 (before treatment) must be performed within 48 hours prior to study treatment administration, unless otherwise indicated in the schedule of assessments, to

confirm to the patient if treatment can be followed up. 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), except for the time window for the End of Treatment visit tumor biopsy that should be collected at Day 15 (+ 1 day). If post-treatment biopsy cannot be performed within + 1 day from last day of treatment (that is, on D15 or D15+1), treatment will be extended to 16 days and surgery or biopsy will be performed the day after.

The summary of study assessments is included in **Appendix *1*: Schedule of study assessments and procedures.**

6.3 Demographic data and medical history

Demographic data include age, sex, and self-reported race/ethnicity. Medical history comprises clinically significant diseases, surgical interventions, history of cancer (including prior antineoplastic treatments and procedures), history of smoking, alcoholism, drug addiction, as well as any medications (i.e., prescribed drugs, over-the-counter drugs, medicinal plants, homeopathic remedies, or food supplements) used by the patient in the 7 days prior to screening visit.

6.4 Tumor assessments

Assessment of primary tumor and regional lymph nodes must be performed by physical examination at screening and prior to administration of study treatment.

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.

6.4.1 Ki67 score assessment

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. For patients with basal Ki67 ≥20% according to local analysis, Ki67 ≥10% will be centrally confirmed retrospectively after inclusion. For patients with basal Ki67 levels between 10% and 19% according to local analysis, Ki67 ≥10% will need to be centrally confirmed before randomization.

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

6.4.2 Tumor imaging assessment by ultrasound

Breast ultrasound and axillary node lymph status assessment should be performed according to institutional practice and result must be known at screening to assess eligibility and tumor size prior to randomization.

All known sites of disease must be documented at screening. Baseline staging to document absence of metastatic disease should be performed as per institutional practice, in alignment with

national guidelines, in patients where there may be a reasonable suspicion of advanced disease (e.g., clinically positive axillary lymph nodes, signs and symptoms). If done, it must be performed within 28 days prior to randomization and reports of these examinations must be available at site. Examination type for tumor staging is at the discretion of the investigator and can include i.e. X-ray, sonography, bone scan, CT, MRI, and/or PET-CT scan.

Patients diagnosed with multifocal or multicentric breast cancer will be eligible for the study if the two largest lesions meet pathologic criteria for ER positivity and HER2 negativity and at least one tumor lesion measures ≥ 1cm in the longest diameter by ultrasound (reference lesion) and this one meets the histologic inclusion criteria of Ki67 score ≥10% as described in Section 6.4.1.

6.5 Safety and tolerability assessments

6.5.1 Laboratory assessments

Laboratory tests will be performed in accordance with local standard treatment and clinical indications before treatment administration. These values should include: hematological test (hemoglobin, hematocrit, red blood cell count, platelet count, WBC and differential count [ANC, lymphocytes, monocytes, eosinophils and basophils, and other cells]); coagulation (INR, PTT (or aPTT)); chemistry panel (serum or plasma): sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin (if total bilirubin is 2xULN, also direct bilirubin), AST, ALT, ALP, urate and LDH; fasting lipid panel: cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (after ≥ 8 hours of fasting); urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria), FSH and estradiol. Urinalysis should be performed as clinically indicated during study treatment.

6.5.2 Pregnancy and assessment of fertility

Premenopausal status is 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.

All patients must undergo a serum pregnancy test at screening to confirm eligibility in the trial and within 14 days prior to initiation of study treatment (with result available prior to dosing), and a urine pregnancy test (with results available prior to dosing) within 24 hours prior to study treatment initiation.

All patients 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 60 days

following cessation of therapy (for patients in the tamoxifen arm). They must, as well, agree to refrain from donating eggs during the same period.

Examples of non-hormonal contraceptive method with a failure rate of <1% per year are 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 post ovulation methods) and withdrawal are not adequate methods of contraception.

An additional pregnancy test is indicated in the EoT visit and in the EoS visit, when a urine pregnancy test should be performed.

In case of pregnancy during study treatment or within 10 days after the last dose of study treatment (for patients taking giredestrant) or 60 days following cessation of therapy (for patients in the tamoxifen arm), the patient must permanently stop study treatment immediately and/or withdraw from the trial, and the pregnancy must be reported on the Clinical Trial Pregnancy Form as specified in ***Section 7.2.4.***

6.5.3 Cardiac function monitoring

Cardiac function monitoring consists of a standard 12-lead ECG, and cardiac signs or symptoms collection. All patients must have a standard 12-lead ECG in screening period, maximum 48h before start of treatment dose, in the EoT visit and in the EoS visit. The same method should be used throughout the study for each patient, and preferably performed and assessed by the same assessor.

Single 12-lead ECGs will be obtained as outlined in the schedule of activities using an ECG machine that automatically calculates the heart rate and measures RR interval, QRS interval, QT interval, and QT interval corrected through use of Fridericia's formula (QTcF)/QT interval, PR duration.

Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position. All ECGs are to be obtained prior to other medical procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review all ECG reports. Copies of ECG tracings (paper or digital) will be kept as part of the participant's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. ECG measurement may be performed by an MN professional but reviewed and assessed by the investigator.

Any patient who develops clinical signs or symptoms of cardiac failure should undergo a standard 12-lead ECG, LVEF measurement, and cardiac enzyme assessment.

6.5.4 Physical examination

Assessment of primary tumor and regional lymph nodes must be performed by physical examination at screening and prior to administration of study treatment.

A complete physical examination should also include an examination of head, eyes, ears, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, digestive, genitourinary, and neurological systems. Changes to abnormalities identified during the baseline period should be recorded at all subsequent physical examinations. New or worsening abnormalities should be recorded as AEs, if applicable.

6.5.5 Vital signs

These will include the measurement of height (only during screening), weight, respiratory rate, heart rate, blood pressure, and body temperature. Abnormal or significant changes in vital signs from baseline should be recorded as AEs, if appropriate.

6.5.6 ECOG performance status

Performance status will be determined using the ECOG performance status scale (see **Table 4)**. Wherever possible, the patient's performance status should always be assessed by the same personnel throughout the study.

Table 4. ECOG performance status scale.

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

http://www.ecog.org/general/perf_stat.html

6.6 Tumor and blood samples

All patients will be required to provide a pre-treatment tumor tissue sample and blood samples during screening, and a tumor biopsy sample and a blood sample on Day 15 (+ 1-2 days) at the end of study treatment.

6.6.1 Tumor tissue samples

Mandatory biopsy samples will be collected before the start of treatment (up to a maximum of 8 weeks before the first dose of study drug). 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. Additional biopsy will be taken at the EoT (+ 1 day) after the last dose of study drug.

Note: if post-treatment biopsy cannot be obtained within + 1 day from last day of treatment (on D15 or D15+1), 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).

Tumor samples obtained are to be collected as tumor paraffin embedded block (two formalin fixed paraffin-embedded blocks [FFPE]). Tumor tissue samples must be of good quality based on total and viable tumor content: Samples must contain a minimum of 500 viable tumor cells that preserve cellular context and tissue architecture. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), punch, or forceps biopsy are acceptable.

Note: Details regarding Ki67 staining can be found in the separate laboratory manual.

Note II: Samples must contain a minimum of 500 viable tumor cells. In the event of containing less cells (but as long as there's a minimum of 350 viable cells), the case can be discussed with the medical monitor and a second FFPE block can be sent to the Sponsor's designated central laboratory.

These samples will be used for assessing study co-primary endpoints referring to changes in tumor cell proliferation as measured by Ki67 expression between baseline and day 15 post-treatment tumor biopsy samples by central assessment in patients with centrally confirmed Ki67 ≥10% (Arm A vs Arm B), and other secondary endpoints as indicated in the protocol.

6.6.2 Blood samples

Mandatory liquid biopsies will be taken before the start of study treatment (up to a maximum 14 days before the first dose of the study drug) and, if possible, at the same timepoint as baseline hematological laboratory assessments, and at the EoT (+ 1 day after the last dose of study drug, which will be D15, D15+1, D16+1). Post-study treatment liquid biopsy samples will be taken at the same timepoint, if possible, as post-study treatment tumor biopsies.

These samples will be used to perform a plasma endocrine panel with samples pre- and post-therapy. Please refer to the study laboratory manual for more information.

Since the identification of new markers that correlate with disease activity and the efficacy or safety of treatment is rapidly developing, the definitive list of analyses remains to be determined.

6.7 Patient discontinuation

Patients have the right to withdraw from the study at any time for any reason. 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.

Should a patient decide to withdraw, all efforts should be made to complete and report the observations as thoroughly as possible. Although the patient has no obligation to provide the reasons for his/her voluntary withdrawal, 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 discontinuation from the study should be made. The principal specific reason for the removal of a patient from the study must be clearly stated in his/her medical records and will be recorded on the CRF.

In the case that the patient decides to prematurely discontinue study treatment, he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the CRF.

6.8 Study and site discontinuation

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.
- Data recording is inaccurate or incomplete.
- Excessively slow recruitment.
- Poor protocol adherence.
- Non-compliance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP).

7 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

Safety assessments will consist of monitoring and recording protocol-defined AEs, SAEs and non-serious adverse events of special interest (AESIs); measurement of protocol-specified hematology, clinical chemistry, measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

7.1 AEs definition

An AE is any untoward medical occurrence in a clinical study subject/patient administered a pharmaceutical product, which does not necessarily have a causal relationship with his/her treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, regardless of whether it is considered related to the medicinal (investigational) product.

The causal relationship between an AE and the IMP will be defined as below:

Not related: The temporal association between the adverse event and the IMP makes a causal relationship unlikely, or the subject/patient's clinical state or the study procedure/conditions provide a sufficient explanation for the adverse event.

Related: The temporal association between the adverse event and the IMP makes a causal relationship possible and the subject/patient's clinical state or the study procedure/conditions do not provide a sufficient explanation for the adverse event.

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the IMP drugs.

The descriptions and grading scales found in the revised NCI-CTCAE v 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE v 5.0 can be downloaded from the CTEP website (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf).

The intensity (severity) of an AE will be recorded as one of the following but also CTCAE Grade will be recorded:

- Mild - Easily tolerated and does not interfere with normal daily activities, CTCAE Grade 1.
- Moderate - Causes some interference with daily activities, intervention or treatment may be needed. CTCAE Grade 2.
- Severe - Normal daily activities are substantially impaired, hospitalization and/or intervention or treatment is required, CTCAE Grade 3 or 4.
- Fatal - Death, CTCAE Grade 5.

- Not applicable (clinically significant and asymptomatic laboratory test abnormalities or abnormal assessments, for which no CTCAE grading guidance is applicable but which are considered as AEs).

A mild, moderate or severe AE may or may not be serious (see definition below). These terms are used to describe the intensity of a specific AE. However, a severe AE (such as severe headache) may be of relatively minor medical significance and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

7.1.1 SAEs definitions

Per definition, a SAE is defined as any adverse event that either:

- results in death (i.e., the AE actually causes or leads to death),
- is life threatening (i.e., the AE, in the view of the investigator, places the subject/patient at immediate risk of death when it occurs),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person ability to conduct normal life functions),
- is a congenital anomaly/birth defect (in a neonate/infant born to a mother exposed to the investigational product(s).

7.1.1.1 Definition of life threatening

An AE is life threatening if the subject/patient was at immediate risk of death from the event as it occurred, i.e. does not include an event that might have caused death if it had occurred in a more serious form. For instance, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis can be fatal.

7.1.1.2 Definition of hospitalization

AEs requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject/patient has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment which would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not to be notified according to immediate reporting criteria. If anything untoward is reported during any procedure, this must be reported as an AE and either ‘serious’ or ‘non-serious’ attributed according to the usual criteria.

7.1.1.3 Definition of clinically/medically significant event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clinically/medically significant events MUST be reported as SAEs.

In this clinical trial and as defined in this protocol, SAEs and hospitalizations unequivocally and solely related to established tumor disease progression will NOT be treated as SAEs for reporting obligations.

SAEs, if brought to the attention of the Investigator at any time after the cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment (so, in fact serious adverse reactions), will be reported to the Sponsor.

7.1.1.4 Cases of overdose, medication error, drug abuse, or drug misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose.
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose.
- Medication error: accidental deviation in the administration of a drug, including accidentally omitted doses. In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm.
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse. In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

Special situations are not in themselves AEs but may result in AEs. Each AE associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfils seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event). As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the

accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

In the event of an overdose, the investigator should follow the steps described in ***Section 5.6***.

7.1.2 AESIs for IMPs

AESIs must be reported by the Investigator to the Sponsor expeditiously (see ***Section 7.2.1 for reporting instructions***), regardless of their seriousness (i.e., no more than 24 hours after learning of the event). AESIs for giredestrant are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see **Table 5. Guidelines for Management of Patients Who Experience Adverse Events Associated with Giredestrant (GDC-9545).** in ***Section 7.2***).
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Grade ≥3 hepatitis or elevations in AST or ALT.
- Grade ≥3 acute kidney injury, creatinine increases, or renal toxicity.
- Grade ≥2 bradycardia.
- Grade ≥2 thromboembolic events.

7.2 Safety profile and management of AEs for IMPs

AEs will be collected from the first study-mandated procedure until the End of Study visit to be done 28 days (± 3 days) after the last day of study treatment. All study subjects/patients will be carefully monitored for the occurrence of AEs during this period.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible. Any additional events that fall outside this definition should also be reported separately.

All AEs must be recorded in the CRF. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

Table 5. Guidelines for Management of Patients Who Experience Adverse Events Associated with Giredestrant (GDC-9545).

Adverse Reaction	Event action to be taken
Elevation of hepatic transaminases	
General guidance	• If patient presents with jaundice, coagulopathy, abdominal pain, or other symptoms suggestive of hepatic toxicity, perform liver function tests with additional evaluation per institutional guidelines. • If hepatic enzymes are elevated with no obvious malignant cause found, consult with hepatologist. • Treat patient with hepatic enzyme elevation according to local standard of care.
Grade 1 or 2	• Continue giredestrant (GDC-9545). • Rule out alternative etiologies (e.g., disease progression, concomitant medications, or biliary obstruction). • Treat patient according to local standard of care.
Grade 3	• Permanently discontinue giredestrant (GDC-9545). • Consult with hepatologist.
Grade 4 or meets criteria as defined by Hy's Law*	• Permanently discontinue giredestrant (GDC-9545). • Consult with hepatologist.
Gastrointestinal events (nausea, vomiting, diarrhea)	
General guidance	• Monitor closely for GI symptoms. If patient presents with nausea, vomiting, or diarrhea, manage according to local standard of care, including use of anti-diarrheal agents and supportive care such as hydration and dietary modification as appropriate. • Infectious or alternate etiologies should be ruled out.
Grade 2	• Manage and treat according to local standard of care. If persistent despite appropriate medical therapy, withhold giredestrant (GDC-9545) until resolution to Grade ≤ 1.
Grade ≥ 3	• Withhold giredestrant (GDC-9545) until event resolves to Grade ≤ 1. • Manage and treat patient according to local standard of care. • Consider consulting with gastroenterologist. • Resume giredestrant (GDC-9545) at full dose once the event resolves to Grade ≤ 1. • If adverse event is recurring and patient cannot tolerate treatment, then permanently discontinue giredestrant (GDC-9545).

Adverse Reaction	Event action to be taken
Venous thromboembolic events (including pulmonary embolism)	
General guidance	• Advise patient to seek immediate medical attention if they become aware of any symptoms of PE or DVT, such as acute onset of chest pain, shortness of breath, or swelling in extremities.
Grade ≥ 2	• Withhold giredestrant (GDC-9545) until patient is stable. • Manage and treat patient according to local standard of care. • Resume giredestrant (GDC-9545) at full dose once the patient is stable. • Permanently discontinue giredestrant (GDC-9545) for recurrent thromboembolic events.
Bradycardia	
General guidance	• Monitor patient closely for symptomatic bradycardia.
Grade 1	• Continue giredestrant (GDC-9545). • Continue to monitor patient per schedule of activities. • If heart rate falls below 40 bpm, withhold giredestrant (GDC-9545) until heart rate returns to > 40 bpm and patient remains asymptomatic.
Grade 2	• Withhold giredestrant (GDC-9545) and consult with cardiologist. • Resume giredestrant (GDC-9545) at full dose once the event improves to Grade ≤ 1 and the heart rate returns to >40 bpm. • For recurrent Grade 2 bradycardia, permanently discontinue giredestrant (GDC-9545).
Grade ≥ 3	• Permanently discontinue giredestrant (GDC-9545) and consult with cardiologist.
Renal toxicity or increased creatinine	
Grade 1 or 2	• Continue giredestrant (GDC-9545). • Manage patient according to local standard of care.
Grade ≥ 3	• Permanently discontinue giredestrant (GDC-9545). • Manage patient according to local standard of care. • Consult with nephrologist.
Non-hematologic toxicity	
Grade 1 or 2	• Continue giredestrant (GDC-9545). • Rule out alternative etiologies.
Grade 3	• Withhold giredestrant (GDC-9545) until symptoms resolve to Grade ≤ 1, and then resume giredestrant (GDC-9545) at full dose.
Grade 4	• Permanently discontinue giredestrant (GDC-9545).

DVT = deep vein thrombosis; GI = gastrointestinal; PE= pulmonary embolism; ULN = upper limit of normal.

*The finding of an elevated ALT or AST (> 3xULN) in combination with either an elevated total bilirubin (> 2xULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law).

7.2.1 AEs and SAE reporting and timeframe

Reporting requirements will comply with all EU safety reporting requirements as detailed in "Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC".

The investigator is responsible for ensuring that all adverse events (see Section 7.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness, severity and causality.

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.

The investigator or investigator's team will report all protocol defined SAEs and AESIs to the Sponsor (MEDSIR) no later than 24 hours of any site study team staff becoming aware of the event as follows:

- The full details of the SAE and/or AESI should be collected and fully documented using the SAE form and sent to MEDSIR.
- Follow-up information, copies of the results of any tests, the outcome of the event plus the investigator's opinion of IMP relationship to the SAE(s) and AESI(s), and other document when requested and applicable, will accompany the SAE form as available on the day of reporting or provided as soon as possible thereafter.
- The original SAE Report Form and the fax confirmation sheet from the Sponsor must be kept with the CRF documentation at the study site(s).

All SAE forms will be sent by the investigator or investigator's team to the Sponsor (MEDSIR) according to the reporting instructions provided by MEDSIR at the site initiation visit and filed in the Investigator's File.

All SAEs must be reported to Drug Safety Evaluation (DSE) Clinical Safety and Pharmacovigilance (CSPV) team address: EMPRESS_sae@medsir.org.

SAEs and AESIS will be followed until resolved, a stable outcome or baseline condition is reached, subject/patient is lost to follow-up or dies.

As Sponsor, MEDSIR will be responsible for ensuring that events are reported within the mandated timeframe to the EMA and other Competent Authorities, Institutional Review Boards /Institutional Ethics Committees (IRBs/IECs) and investigator(s), as necessary and in accordance with all applicable guidelines, approved directives, and regulations. All safety reporting local regulatory requirements will be followed.

7.2.2 Expedited reporting to Health Authorities, Investigators, IRBs, and IECs

To determine reporting requirements for single SAE cases, MEDSIR (as Sponsor) or its designee will assess the expectedness of these events using the following reference documents:

- Current IMP SmPC/IB.

MEDSIR (as Sponsor) or its designee will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Within 7 calendar days after being notified of the event, MEDSIR (as Sponsor) or its designee will report unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities, to the investigators and IRBs/IECs. MEDSIR (as Sponsor) or its designee will report other unexpected SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/IECs by a written safety report within 15 calendar days of notification. All safety expedited reports will be reported in accordance to all regulatory reporting obligations (including timelines) and local regulatory requirements.

7.2.3 Other safety-related reports

As Sponsor, MEDSIR will assess constantly the benefit/risk rate of the trial, that means a continuous evaluation of the safety profile of the drugs under investigation will be done using all available information. MEDSIR will provide the regulatory agencies and competent authorities and the investigators with any relevant information that may affect the benefit/risk rate of the trial. An annual Development Safety Update Report (DSUR safety report) for IMP will be prepared and distributed by MEDSIR or its designee in accordance with all regulatory reporting obligations and local regulatory requirements.

In order to ensure the correct and necessary exchange of safety related information between MEDSIR (as Sponsor) and Roche (as the owner of the IMP), a project specific Safety Data Exchange Agreement will be established and signed between both companies.

MEDSIR or its designee will report any finding of noncompliance (as failure to follow any applicable regulation or institutional policies that govern human subjects' research) and/or serious noncompliance (as noncompliance that materially increases risks that result in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants) according to any reporting obligation and local regulatory requirements.

7.2.4 Pregnancy reporting

Irrespective of the treatment received by the subject/patient, any subject/patient's or subject/patient's partner pregnancy occurring during study treatment or within 10 days after the

last dose of study treatment (for patients taking giredestrant) or 60 days following cessation of therapy (for patients in the tamoxifen arm) must be reported within 24 hours of investigator's knowledge of the event.

Patients will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the final dose of study drug.

Pregnancies will be treated as SAEs and the investigator will complete a Clinical Trial Pregnancy Reporting Form and forward it to the Sponsor according to the reporting instructions provided by MEDSIR at the site initiation visit and filed in the Investigator's File. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

The subject/patient will be asked to provide follow-up information on the outcome of the pregnancy, including premature termination should the case arise and on the infant until 12 months of life. Spontaneous miscarriage and congenital abnormalities will also be reported as SAEs. Follow-up queries may be sent, asking for further information, if required for a comprehensive assessment of the case.

The follow-up period will be deemed to have ended when the health status of the child has been determined at 12 months of the infant's life.

Additional follow-up information on any IMP -exposed pregnancy and infant will be requested at specific time points (i.e., after having received the initial report, at the end of the second trimester, two weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

8 STATISTICAL CONSIDERATIONS

8.1 Sample size

A total of 92 patients will be enrolled in this trial and randomized 1:1 in the arm A with giredestrant (GDC-9545) (n=46) and the arm B with tamoxifen (n=46), with an expected accrual time of approximately 16 months and an additional 0.5 months for follow-up from end of accrual until EoT. EoS will be 28 days (+/- 3 days) after last dose of study treatment is taken.

8.2 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”).

8.3 Populations for Analyses

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]

[redacted]

[redacted]

[redacted]

8.4 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.

8.5 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.

8.6 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 analysed.
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 analyse 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. Because of the non-asymptotic distribution of data, power transformations will be conducted with response and covariate. The transformed values of the Ki67 score are assumed to be a linear function of the treatment as:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2$$

where

Y = The Ki67 score after the treatment,

β_0 denotes intercept,

β_1 denotes the treatment effect,

X_1 refers to the treatment groups (Giredestrant (GDC-9545) and tamoxifen),

β_2 denotes the Ki67 baseline score effect,

X_2 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 analyse observed valid cases for mITT and PP analysis set. Alternatively, the missing management method for ITT analysis will be the multiple imputation.

Table 6. 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.	Supportive -Linear regression (Wald test) adjusted by baseline scores

ID	Set	Analysis sets	Main estimate and (Imputation Method)	Type of analysis
			-Box-cox transformation (Multiple imputation)	
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

CI: Confidence interval; HL: Hodges–Lehmann method; ITT: Intention to treat; mITT: Modified intention to treat; PP: Per protocol.

8.7 Secondary and subgroup analyses

The secondary efficacy endpoints will be done for the mITT analysis set. We only will analyse 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. Power transformations will be deliberated.

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% Pearson-Clopper 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.

8.8 Safety analysis

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

The incidence 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. 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.

[redacted]

8.10 Interim analyses

No interim analyses are planned

8.11 Steering committee

A Steering Committee will be established for this study. It will be composed by the study site investigators, the Sponsor's Medical Monitor, the Scientific Global Coordinator, and additional physicians with experience in experimental therapy management.

Steering Committee meetings are scheduled to review the available safety of the first patient enrolled at each cohort who have completed treatment period, and every 6 months thereafter until communication of the study results. The Steering Committee will meet to review, discuss, and evaluate all the gathered feasibility, safety, and efficacy data. In case of any arising a concern, these meetings can also be called at any time at request of a participating investigator or the Sponsor study team. At these meetings, the Sponsor and the participating investigators must reach a consensus on feasibility, efficacy, and safety data. The Sponsor will prepare minutes from these meetings and circulate them to each investigator for comment prior to finalization.

Each study site investigator will monitor patient's data for serious toxicities on an ongoing basis.

9 ETHICAL CONSIDERATIONS

9.1 Regulatory and ethics compliance

The study will be performed and reported in accordance with the guidelines of the International Conference on Harmonization (ICH), and the ethical principles laid down in the Declaration of Helsinki. The study will be also compliance with European Directive 2001/20/EC and any applicable local regulations.

9.2 IRBs/IECs

Conduct of the study must be approved by an appropriately constituted IRB/IEC. Approval is required for the study protocol, protocol amendments, informed consent forms, study subject information sheets, and advertising materials. The IRB/IEC must also be contacted in the event of any major protocol violation or any SAE.

It is the Investigator's responsibility to communicate with their local IRB/IEC to ensure accurate and timely information is provided at all phases during the study.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC/CA of any protocol amendments (approval is required before implementation of substantial amendments).

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC/CA all unanticipated problems involving risk to human patients. Some IRBs/ECs/CA may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written safety reports or other safety related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC/CA and archived in the site's study file.

9.3 Informed consent

For each study subject, written informed consent will be obtained prior to any protocol related activities. As part of this procedure, the study site Investigator or designee must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drugs in such a manner that the study subject is aware of the potential risks, inconveniences, or adverse effects that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. The subject will receive all information that is required by local regulations and ICH guidelines.

The Consent Form must be signed and dated by the patient or the patient's legally authorized representative before her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative, if applicable.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved Informed Consent Form must be provided to the Sponsor for regulatory purposes.

9.4 Data protection

The Sponsor will ensure the confidentiality of patient's medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data [95/46/EC] confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, the Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

10 SOURCE DOCUMENTATION, STUDY MONITORING AND QUALITY ASSURANCE

10.1 Source data documentation

Source data refers to all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents are original documents, data, and records (i.e., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

Sponsor's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

At a minimum, source documentation must be available to substantiate subject identification, eligibility, and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; adequate reporting and follow-up of AEs; administration of concomitant medication; study receipt/dispensing/return records; study administration information; and date of completion and reason.

Data recorded on the CRF will be verified by checking the CRF entries against source documents (i.e., all original records, laboratory reports, medical records) in order to ensure data completeness and accuracy as required by study protocol. The Investigator and/or site staff must make CRFs and source documents of subjects enrolled in this study available for inspection by MEDSIR or its representative at the time of each monitoring visit.

The source documents must also be available for inspection, verification, and copying, as required by regulations, officials of the regulatory health authorities (i.e., FDA, EMEA, and others), and/or ECs/IRBs. The Investigator and study site staff must comply with applicable privacy, data protection, and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

The patient must also allow access to the patients' medical records. Each patient should be informed of this prior to the start of the study.

10.2 Study monitoring and source data verification

Study progress will be monitored by MEDSIR or its representative (i.e., a CRO) as frequently as necessary to ensure:

That the rights and well-being of human subjects are protected;

- the reported trial data are accurate, complete, and verifiable from the source documents; and

- the conduct of the trial is in compliance with the current approved protocol/amendment(s), GCP, and applicable regulatory requirements.

Contact details for the team involved in study monitoring will be identified in a handout located in the Investigator Site File.

Data recorded on the CRF will be verified by checking the CRF entries against source documents (i.e., all original records, laboratory reports, medical records, subject diaries) in order to ensure data completeness and accuracy as required by study protocol. The Investigator and/or site staff must make CRFs and source documents of subjects enrolled in this study available for inspection by the Sponsor or its representative at the time of each monitoring visit.

10.3 Retention of records

Investigators must retain all study records required by the applicable regulations in a secure and safe facility. The Investigator must consult a Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location, disposition, or custody of the study files.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable e regulatory requirements or by an agreement with the Sponsor. The CHMP requires retention for the maximum period of time permitted by the institution, but not less than 15 years (ICH E6, 4.9.5). It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained (ICH E6, 5.5.12).

The study site Investigator must not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The study site Investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor and the FDA and/or EMA (or respective individual EU country regulatory authorities).

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

10.4 Data quality assurance

During and/or after completion of the study, quality assurance auditor (s) named by the MEDSIR or the regulatory authorities may wish to perform on-site audits. The Investigators will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

The Sponsor's representatives are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (i.e., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH E6 Good Clinical Practice (GCP) and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's (or designee's) Quality Assurance Department. Inspection of site facilities (i.e., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP (ICH E6), and applicable country regulatory requirements.

11 DATA MANAGEMENT

11.1 Data entry and management

In this study, all data will be entered onto CRFs in a timely fashion by the Investigator and/or the Investigator's dedicated site staff.

The Investigator must review data recorded in the CRF to verify their accuracy.

Reconciliation of the data will be performed by the designated CRO. At the conclusion of the study, the occurrence of any protocol violations will be identified and recorded as part of the clinical

database. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and will become available for statistical data analysis.

11.2 Data clarification

As part of the conduct of the trial, MEDSIR may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query.

11.3 Data coding procedures

Coding of AEs, medical history, and prior and concomitant medications will be performed using standard dictionaries as described in the Data Management Plan.

12 STUDY MANAGEMENT

12.1 Discontinuation of the study

MEDSIR reserves the right to discontinue the study for safety or administrative reasons at any time. Should the study be terminated and/or the site closed for whatever reason, all investigational drugs pertaining to the study must be returned to MEDSIR. Any actions required to assess or maintain study subject safety will continue as required, in spite of termination of the study.

12.2 Changes to the protocol

Any change or addition to this protocol requires a written protocol amendment or administrative letter that must be approved by MEDSIR, the Scientific Global Coordinator, the study site Investigator, and the IRB/IE/CA before implementation. This requirement for approval should in no way prevent any immediate action from being taken by the study site Investigator or MedSIR in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the study site Investigator and is implemented for safety reasons, MEDSIR should be notified as soon as possible (within 24 hours if possible) and the IRB/IEC/CA should be informed as necessary.

12.3 Publication policy protection of trade secrets

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without prior written permission from the Scientific Global Coordinator and MEDSIR However, authorized regulatory officials, the Scientific Global Coordinator or the study site Investigator, and MEDSIR personnel (or their representatives) will be allowed full access to inspect and copy the records. All clinical investigational drug, patient bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Scientific Global Coordinator or the study site Investigator and MEDSIR.

The Sponsor will ensure that as far as possible results of this study will be published as scientific/clinical papers in high-quality peer-reviewed journals. Preparation of such manuscripts will be made with full collaboration of principal Investigators and in accordance with the current guidelines of Good Publication Practice.

The Sponsor must be notified of any intent to publish data collected from the study and prior approval from Sponsor must be obtained prior to publication.

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Appendix 1: Schedule of study assessments and procedures

Study Period	**Screening Period***	**Treatment Period****		**End of Treatment visit****	**Post-Treatment End of Study visit**
Day	**-28 to -1 day**	**Baseline (Day 1)**	**Days 2-15**	**Day 15 (+ 1 day)**	**28 days (+/- 3 days) after last dose of study treatment**
Informed Consent Form[1]	x				
Demographic data and medical history[2]	x				
ECOG performance status	x	x		x	x
Weight and vital signs[3]	x	x		x	x
ER, PgR and HER2 status[4]	x				
Ki67 score assessment[5, 14]	x			x	

Study Period	**Screening Period***	**Treatment Period****		**End of Treatment visit****	**Post-Treatment End of Study visit**
Day	**-28 to -1 day**	**Baseline (Day 1)**	**Days 2-15**	**Day 15 (+ 1 day)**	**28 days (+/- 3 days) after last dose of study treatment**
Breast ultrasound and axillary lymph node status[6]	x			x (as clinically indicated)	
Tumor staging as per institutional practice[7]	x				
Complete physical examination (breast and regional lymph nodes examination)[8]	x	x		x	x
AE reporting[9]	x	x	x	x	x
Concomitant medication reporting[10]	x	x	x	x	x
12-Lead ECG[11]	x	x		x	x
Laboratory assessments[12]	X	x		x	x

Study Period	**Screening Period***	**Treatment Period****		**End of Treatment visit****	**Post-Treatment End of Study visit**
Day	**-28 to -1 day**	**Baseline (Day 1)**	**Days 2-15**	**Day 15 (+ 1 day)**	**28 days (+/- 3 days) after last dose of study treatment**
Pregnancy test[13]	X	x		x	x
Tissue and blood samples collection[14]	x			x	
Viral serology[15]	x				
Treatment administration[16]		x	x (administered at home)	x	
Medication diary[17]		x		x	
Post-study anticancer therapy					x

**Screening period:* *all screening data needs to be completed 48h prior to randomization to allow enough time for medical monitor review.*

***Treatment period and EoT visit:** After confirming eligibility through the screening process as indicated above, patients will be scheduled for baseline visit at Day 1 of treatment within 48 h after randomization. If post-treatment surgery or biopsy cannot be performed within + 1 day from last day of treatment (that is, on Day 15 or the immediate day after [Day 15+1]), treatment will be extended to a total of 16 days and patients will be able to have surgery or biopsy the following day (be it Day 15 + 2).*

1. **Informed Consent Form:** Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening, unless otherwise indicated.
2. **Demographic data and Medical history:** Complete medical history and demographics (including age, gender, and ethnic origin). All medications taken in the last 28 days prior to enrolment will be collected.
3. **Weight and vital signs**: Weight, height (only at screening), respiratory rate, blood pressure measurements (systolic and diastolic), pulse rate, and body temperature (oral, axillary, or tympanic temperature).
4. **ER, PR and HER2 status:** Local confirmation of ER[+] (<= 500 cell count) and HER2[-] status based on local testing on the most recent analyzed biopsy.
5. **Ki67 score assessment:** Ki67 will be analyzed locally at the time of inclusion. For patients with basal Ki67 ≥20% according to local analysis, Ki67 ≥10% will be centrally confirmed retrospectively after inclusion. For patients with basal Ki67 levels between 10% and 19% according to local analysis, Ki67 ≥10% will need to be centrally confirmed before inclusion. Ki67 will be analyzed centrally on the post-treatment biopsy.
6. **Breast ultrasound and axillary node status**: Breast and axillary ultrasound should be performed according to institutional practice and result must be known at screening to assess eligibility and tumor size prior to randomization, and then as clinically indicated.
7. **Tumor staging as per institutional practice**: Baseline staging to document absence of metastatic disease should be performed as per institutional practice, in alignment with national guidelines, in patients where there may be a reasonable suspicion of advanced disease (e.g., clinically positive axillary lymph nodes, signs and symptoms). If done, it must be performed within 28 days prior to randomization and reports of these examinations must be available at site. Examination type for tumor staging is at the discretion of the investigator and can include i.e. X-ray, sonography, bone scan, CT, MRI, and/or PET-CT scan.

8. **Complete physical examination:** including complete evaluation of the breast primary tumor and regional lymph nodes and evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

9. **AE reporting:** After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported with grading according to the NCI–CTCAE v.5.0 criteria. After initiation of study drug, all adverse events will be reported until 28 days (EoS) after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment.

10. **Concomitant medication reporting:** Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 14 days prior to initiation of study drug until end of study visit.

11. **12-lead ECG:** Patients should be resting in a supine position for at least 10 minutes prior to ECG recording. All ECGs will be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). All patients must have a standard 12-lead ECG in screening period, maximum 48h before start of treatment dose, in the EoT visit and in the EoS visit.

12. **Laboratory assessments:** These values should include: hematological test (hemoglobin, hematocrit, red blood cell count, platelet count, WBC and differential count [ANC, lymphocytes, monocytes, eosinophils and basophils, and other cells]); coagulation (INR, PTT (or aPTT)); chemistry panel (serum or plasma): sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin (if total bilirubin is 2xULN, also direct bilirubin), AST, ALT, ALP, urate and LDH; fasting lipid panel: cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (after ≥ 8 hours of fasting); urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria), FSH and estradiol. Baseline (Day 1, prior to initiation of study treatment) laboratory assessments are not required if the screening assessments were performed at within 14 days prior to initiation of study treatment.

13. **Pregnancy test:** 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. An additional pregnancy test is indicated in the EoT visit and in the EoS visit, when a urine pregnancy test should be performed.

14. **Tissue and blood samples collection:** Mandatory tumor tissue biopsy samples will be collected before the start of treatment (up to a maximum of 8 weeks before the first dose of study drug). 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. A fresh post-study treatment biopsy will be obtained on Day 15 (+ 1 day). A fresh post-study treatment biopsy will be obtained on D15 (+1 day). If post-treatment surgery cannot be performed within + 1 day from last day of treatment (that is, on D15 or D15+1), treatment will be extended to 16 days and surgery or biopsy can be performed on the following day. At both timepoints the most recent tumor biopsy from the patient should be obtained when available. Mandatory liquid biopsy samples will be obtained before the start of study treatment (up to a maximum of 14 days before the first dose of study drug) and, if possible, at the same timepoint as baseline hematological laboratory assessments. Post-study treatment liquid biopsy samples will be taken at the same timepoint, if possible, as post-study treatment tumor biopsies.

15. **Viral serology:** Human Immunodeficiency Virus, Hepatitis B surface Antigen (HBsAg), total Hepatitis B core Antibody (HBcAb), Hepatitis C Virus antibody; additional tests for Hepatitis B Virus DNA or Hepatitis C Virus RNA will be required to confirm eligibility.

16. **Treatment administration:** Patients will receive either giredestrant (GDC-9545) 30 mg, PO, QD on days 1-15 – Arm A - or tamoxifen – Arm B - 20mg, PO, QD on days 1-15. Treatment on Day 1 will be administered at the clinic. If post-treatment surgery or biopsy cannot be performed within + 1 day from last day of treatment (that is, on Day 15 or Day 15+1), treatment will be extended to 16 days so that surgery or biopsy can be performed on the following day.

17. **Medication diary:** Patients will receive a medication diary and should be instructed to complete the medication diary each day (Day 1 to Day 15, or Day 16 if applicable). The medication diary and unused capsules or tablets in their bottles should be collected and reviewed at the EoT visit for drug accountability.