CT application(s) summary report

- **Protocol title:** A Phase 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
- **Protocol code number:** WO43571
- **Eudra-CT:** 2022-500014-26-00
- **Version:** 4.0
- **Date:** 28-June-2023

- **Investigational Medicinal Product being tested:**

Biological ☐ **Pharmaceutical** ■ **Innovative** ☐

Herbal medicine ☐ **Medical device** ☐

- **Trade Name:** NA
- **IMP Authorization Status in Egypt:** not authorized
- **Pharmaceutical Form:** Oral Capsules
- **Active Substance Name:** Giredestrant
- **Type:** Pharmaceutical
- **IMPD Quality Dossier Decision:** Accepted
- **Date of Quality Administration**: 19-March-2024

- **Sponsor:** F Hofmann La Roche Ltd
- **CRO:** NA

- **Indication:** Previously Untreated Her2-Positive, Estrogen Receptor-Positive Locally Advanced or Metastatic Breast Cancer

- **Investigator's brochure (IB)**

Version: 7.0
Date: May 2023

- **Name of all Sites:**
  1. National cancer institute
  2. Dar Al Salam Hospital
  3. Sohag Oncology Hospital
- **Name of PI(s):**
  1. Dr. Emad Shash
  2. Dr. Ahmed Abdelaziz
  3. Dr. Ahmed El Sayed

- **EDA approval date:** 08-April-2024

- **Summary of pre-clinical studies:**
  1. **Primary Pharmacodynamics**

- **In Vitro Studies**

Cellular Assay for Nuclear Hormone Receptor Selectivity (Study 17-0012)

Giredestrant was tested for inhibition against a panel of 25 nuclear hormone receptors using cell-based reporter assays. Giredestrant caused a 96%−97% inhibition of ERα and ERβ at a concentration of 0.1 and 1 μM. None of the other nuclear hormone receptors that were evaluated exhibited more than 6% inhibition at 0.1 μM or more than 30% inhibition at 1 μM

ERα Protein Degradation (Study 17-0009)

Giredestrant caused a reduction in ERα protein levels in MCF7 cells expressing exclusively ERα WT, and in MCF7 cells engineered to co-express ERα Y537S protein. For MCF7 cells expressing only ERα WT, the mean EC50 for ER depletion was 0.059 ±0.012 nM, achieving a relative maximum degradation of 106.9%± 2.6% (the level of ERα following treatment with 5 nM Fulvestrant was used to define 100% degradation). For MCF7 cells expressing the ERα Y537S mutant, the mean EC50 value was 0.170 ± 0.031 nM with a relative maximum degradation of 113.0%± 2.1%. Western blot analysis showed that co-treatment of Giredestrant with the proteasome inhibitor MG-132 attenuated Giredestrant-mediated ERα depletion, suggesting that Giredestrant causes ERα degradation that is dependent on the 26S proteasome.

In Vitro Anti-Proliferation Activity of Giredestrant in Breast Cancer Cell Lines (Study 17-0010)

Giredestrant was shown to inhibit the proliferation of 8 different ER+ human breast cancer cell lines grown in the absence or presence of 0.1 nM E2, with IC_{90} values ranging between 0.8 and 13.6 nM in the presence of E2.

In Vitro Combination of Giredestrant and Palbociclib (Study 17-0014)

Combining Giredestrant with palbociclib resulted in a greater anti-proliferative effect than could be achieved by either agent alone in ERα WT or Y537S cell lines. Positive Bliss scores were observed at nanomolar concentrations of Giredestrant and palbociclib, implying synergy in these dose ranges.

- **In Vivo Studies**

Giredestrant Efficacy in Combination with Palbociclib (Study 16-3311)

The anti-tumor activity of Giredestrant was also evaluated in combination with the CDK4/6 inhibitor palbociclib. Immunocompromised mice supplemented with subcutaneous estrogen pellets and bearing MCF-7 human xenografts were administered either Giredestrant (3 mg/kg, PO, QD), palbociclib (50 mg/kg, PO, QD), or their combination. As a benchmark comparison, Fulvestrant was dosed subcutaneously at 50 mg/kg on days 1, 3 and 8, and then at 25 mg/kg twice per week, to mimic human exposures, either as a single agent or in combination with palbociclib at 50 mg/kg. Giredestrant treatment resulted in 81% TGI whereas Fulvestrant resulted in 7% TGI, and palbociclib resulted in 43% TGI. The combination of Giredestrant plus palbociclib treatment resulted in TGI of 109%. The combination of Fulvestrant plus palbociclib

resulted in TGI of 41%.

PD Response of Giredestrant in an Immature Rat Uterine Wet Weight Assay (Study 15-0097 K)

The uterus undergoes pronounced morphological changes in response to estrogen and can be leveraged to determine the in vivo estrogenic or anti-estrogenic activity of an agent. Treatment of immature female CRL:CD(SD) rats with known estrogenic compounds 17α- Ethinylestradiol (EE) or tamoxifen resulted in statistically significant increases in uterine wet weight. Giredestrant at 0.1 or 10 mg/kg administered PO, QD for 4 days in the absence of EE resulted in decreased uterine wet weight relative to control uteri. These data are consistent with a full ER antagonism profile for Giredestrant, with no evidence of partial agonism in the uterus.

2. Secondary Pharmacodynamics

- **In Vitro Studies**

In Vitro Secondary Pharmacology: Functional Assays (Studies 15-4062, 16-0961, and 16-0962)

Giredestrant showed an antagonistic effect on human α1A adrenergic receptors with an IC_{50} of 1.3 μM and on human NK1 receptors with an IC_{50} of 9.1 μM. No significant functional effect was observed with Giredestrant at 10 μM on human α2A and α2B adrenergic receptors. The most potent IC_{50} (1.3 μM on human α1A receptors) by Giredestrant on secondary pharmacology is approximately 160-fold higher than the observed C_{max} (unbound) of 8.14 nM at a dose of 30 mg in humans in the Phase I clinical trial.

3. Toxicology and Safety Pharmacology

The nonclinical toxicology program was designed to evaluate the nonclinical safety profile of Giredestrant to support initial clinical trials of QD PO administration of Giredestrant in patients with ER+breast cancer. Rats and monkeys were chosen as appropriate species for toxicity studies based on 1) the ability to obtain sufficient exposure of parent drug, 2) similarity of in vitro metabolic profiles to that of humans 3) the anticipated PD effects of Giredestrant in these species, and 4) similarity of female reproductive cycle and tissue morphology to humans in monkeys. Results from the nonclinical toxicity and safety pharmacology studies completed to date provide a robust characterization of the toxicity profile of Giredestrant to support the administration of Giredestrant to patients with cancer in the ongoing and upcoming clinical trials.

- **Single-Dose Toxicity**

The tolerability and TK profiles of Giredestrant were assessed in female rats administered a single dose of up to 300 mg/kg by oral gavage (Study 15-4013). Giredestrant was well-tolerated at all dose levels tested and there were no mortalities, clinical observations or changes in body weight attributed to Giredestrant. The tolerability and TK profiles of Giredestrant were assessed in female cynomolgus monkeys following a single oral dose of up to 300 mg/kg (Study 15-4262). Giredestrant related clinical signs were limited to vomitus observed at approximately 2 hours post-

dose in females given 300 mg/kg. There were no effects on bodyweight, visual food consumption, hematologic, or clinical chemistry parameters.

- **Repeat-Dose Toxicity**

In repeat-dose general toxicity studies the tolerability and TK profiles of Giredestrant were assessed in female rats (Studies 16-1593 and 18-1170) and monkeys (Studies 16-1594 and 18-1171) for 4- and 26-weeks, respectively. To enable expansion of clinical trial participation to male patients, a 13-week bridging toxicity study was subsequently conducted in male rats (Study 20-0743). Adverse organ effects identified in pivotal toxicity studies were generally dose-responsive, largely confined to the kidney and liver, and monitorable in the clinic using standard laboratory assessments. The findings in reproductive organs in both species are consistent with the anti-estrogenic mode of action of Giredestrant and were partially reversible in both species. In both rats and monkeys, there was a dose-dependent Phospholipidosis (PLD) observed in numerous organs. Major findings are summarized below.

i. Phospholipidosis

Dose-related drug-induced PLD, related to the cationic-amphiphilic structure of Giredestrant, was observed in repeat-dose studies for both rats and monkeys. In the majority of organs and cells affected, no degenerative changes were correlated with the presence of PLD, and thus this finding was considered to be a cellular adaptive response in these tissues (Reasor et al. 2006). In rats, the presence of PLD may have contributed to the toxicity observed in the kidney (males and females) and liver (females). In female monkeys, hepatotoxicity occurred in conjunction with PLD and therefore may also have been associated with PLD. In addition, degeneration of scattered individual muscle fibers with microscopic evidence of PLD was also observed in rats and monkeys, consistent with PLD-associated myopathy. The translatability of PLD from nonclinical species to patients is not certain. Many drugs such as tamoxifen and palbociclib have not demonstrated clinical concerns despite their PLD findings in nonclinical studies. In general, PLD is of greatest concern when accumulations occur in critical cell types such as cardiomyocytes, neurons, and retinal epithelium (Chatman et al. 2009) and PLD was observed in retinal epithelium in the 13- and 26- week rat studies but only at the high dose of 30 mg/kg. No evidence of PLD in retinal pigment epithelium of the eye was observed in either the 4- or 26-week female monkey studies. In the 26- week female monkey study, PLD findings at the lowest dose (7 mg/kg) were limited to minimal changes in the liver and lymph nodes (mandibular and mesenteric). A dose-responsive PLD was prominent in numerous organs, but adverse organ effects were largely confined to the skeletal muscle, kidney and liver. It is unclear whether this will translate into a clinical finding in humans and whether this will have any clinical sequelae if it does.

ii. Hepatic Effects

Dose-dependent hepatic effects were observed in repeat-dose studies in both rats and monkeys given Giredestrant. In female rats and monkeys, clinical and anatomic pathology indicative of hepatotoxicity generally reversed following a recovery period. In the 28-day study where hepatic

toxicity was more prominent in female monkeys, recovery was only assessed at the 60 mg/kg dose level, which did not demonstrate signs of hepatotoxicity during the dosing period.

iii. Renal Effects

Dose-dependent effects on the kidneys were observed in repeat-dose studies in both rats and monkeys given Giredestrant. In ongoing clinical trials, evaluations will include serum creatinine, blood urea nitrogen, and glomerular filtration rates to assess renal function.

iv. Reproductive Effects

Giredestrant-related effects in female reproductive tissues, consistent with the expected pharmacology of Giredestrant on ER degradation, were observed at all doses in both species in the 28-day repeat-dose toxicity studies.

- In the ovaries, multiple ovarian follicular cysts with or without intracystic hemorrhage and correlating with increased ovarian weight was present in both rats and monkeys, and granulosa cell hyperplasia was observed in rats at all doses. Small-sized uterus was observed in all females from all Giredestrant groups.
- In the cervix and vagina, findings consisted of increased epithelial mucification without cornification in rats and atrophic epithelium with reduced or absent vaginal cornification in monkeys. In the mammary gland, findings included hypertrophy/hyperplasia of the acinar and ductal epithelium in rats and hypertrophy/vacuolation of the acinar epithelium and atrophy of the gland/duct in monkey.
- Male reproductive findings in the 13-week toxicity study in male rats included a reduction in prostate gland weight, both in organ-to-body and organ-to-brain ratios at ≥3 mg/kg and an increase in epididymis-to-body relative weight, the latter of which may be related to the observed decrease in body weight.

v. Body Weight and Metabolic Effects

In female rats given Giredestrant for 26 weeks, increased body weight and food consumption was observed in all dose groups and trended toward reversibility during the recovery period. In contrast, there was a significant decrease in body weight gain in male rats given Giredestrant for 13 weeks at ≥3 mg/kg with a mean reduction in body weight relative to controls of 11% and 16% for the 3 and 30 mg/kg cohorts, respectively, which demonstrated trend to reversibility up to 10 mg/kg but persisted in the 30 mg/kg dose group throughout recovery.

vi. Cardiovascular

There were no Giredestrant-associated findings identified in a single dose dedicated cardiovascular safety pharmacology study. The IC_{50} for hERG potassium current inhibition by Giredestrant was determined to be 6.1 µM (Hill coefficient= 1.6), which is 749-fold higher than the observed C_{max} (unbound) of 8.14 nM at a dose of 30 mg in humans for the Phase I clinical trial. Giredestrant-related decreased heart rate and increased RR interval was observed at all doses in the 4- and 26-

week female monkey studies but was not considered adverse, as effects were within historical ranges and were not associated with changes in clinical signs or systemic blood pressure.

4. Genotoxicity

Giredestrant was considered not mutagenic in Salmonella typhimurium strains (TA98, TA100, TA1535 and TA1537) or Escherichia coli (WP2 uvrA) in the absence or presence of an exogenous metabolic activation system (S-9) (Study 16-1269). Treatment of human lymphocytes with Giredestrant in the absence or presence of S9 did not induce an increase in frequency of binucleate cells with micronuclei when tested up to the limit of solubility or cytotoxicity. The frequency of binucleate cells with micronuclei was similar to and not statistically significantly higher than those observed in the concurrent vehicle controls at any concentration analyzed under all treatment conditions (Study 16-1268). A small but statistically significant ($p \leq 0.05$) increase in micronucleus polychromatic erythrocytes was observed solely at the highest dose group (animals treated with Giredestrant at 100 mg/kg/day), no significant increases ($p > 0.05$) were observed at 10 or 30 mg/kg. Micronucleus polychromatic erythrocytes frequencies for all treated animals were considered to be consistent with the concurrent vehicle control data and all values fell within the laboratory's historical control data. The significant increase was considered to be a chance occurrence that was of no biological relevance. Under the conditions of this study, it was concluded that Giredestrant did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of female rats treated up to 100 mg/kg/day.

5. Carcinogenicity

No carcinogenicity studies have been conducted with Giredestrant. As per ICH S9, carcinogenicity studies are not required to support clinical trials conducted in patients with cancer.

6. Reproductive and Developmental Toxicity

Administration of Giredestrant via oral gavage once daily from gestation days (GD's) 7 to 17 was tolerated in pregnant female rats at doses of 3 and 10 mg/kg/day. Giredestrant-related effects on embryo-fetal development at ≥3 mg/kg/day included a low implantation rate, higher post implantation loss and low fetal viability. Occasional malformations of domed heads, meningocoele, and maxillary micrognathia were also observed on external examination. The NOAEL for maternal-fetal toxicity and embryofetal development is considered to be less than 3 mg/kg/day, which provides a 1×AUC-based exposure factor relative to the 30 mg clinical dose.

7. Safety Pharmacology

- **Cardiovascular System**

  In a single-dose telemetry-instrumented female cynomolgus monkey safety pharmacology study (Study 16-1595), there were no Giredestrant-related changes in CV parameters, intra-abdominal body temperature, food consumption, or body weight at any dose level up to the maximum dose tested of 60 mg/kg. However, in 4- and 26-week studies (Studies 16-1594 and 18-1171) there were significant increases in RR-interval at all dose levels. As there were no accompanying

changes in blood pressure and reductions were within historical ranges, they were not considered to be adverse.

- **Central Nervous System**

  A general behavior and neurobehavioral assessment (functional observation battery [FOB]) was integrated in the 4-week general toxicity study in rats with no findings attributed to Giredestrant (Study 16-1593). An assessment of locomotor activity was performed on Day 25-27 at approximately 4 hours post-dose and on Day 24-25 of the recovery phase. There was a significant decrease in locomotor activity observed at the high dose of 100 mg/kg, which was not evident after 4 weeks of recovery. The no-observed-effect level (NOEL) for decreased locomotor activity was 30 mg/kg, corresponding to a mean C_{max} of 1730 ng/mL and an AUC0-24h of 35,100 ng • hr/mL. Neurological examinations were integrated in the 4-week toxicity study in monkeys (Study 16-1594) with no Giredestrant-related effects observed at up to 200 mg/kg (Day 12) and up to 60 mg/kg (Day 24). The Day 24 NOEL corresponds to a mean C_{max} and AUC0-24hr of 841 ng/mL and 16,200 ng • hr/mL, respectively (assessed on Day 28).

- **Respiratory System**

  Assessments of respiratory function were integrated into the 4-week toxicity study in monkeys (Study 16-1594). Oxygen saturation was measured by pulse oximetry and respiratory rates were determined without anesthesia. No Giredestrant−related effects on respiratory function were observed up to 200 mg/kg (Day 13) and up to 60 mg/kg (Day 23).

Toxicology and Safety Pharmacology Integrated Analyses

The toxicology program was designed to evaluate the nonclinical safety and TK profile of Giredestrant. Daily PO administration of Giredestrant was tolerated for up to 26 weeks at doses up to 30 mg/kg in rats and 20 mg/kg in monkeys. Giredestrant was orally bioavailable in both species and systemic exposures similar to or in excess of anticipated therapeutic exposures were achieved in the pivotal repeat dose GLP studies. The doses used in the pivotal toxicity evaluations were appropriate based on evidence of dose-limiting toxicities in both species. In rats, toxicologically significant kidney toxicity was observed at 30 mg/kg (13-week male and 26-week female studies) and significant hepatic toxicity at 100 mg/kg (4- week female study). In monkeys, moribund euthanasia occurred at 60 mg/kg in the 26-week study due to significant body weight loss and inanition.

- **Summary of previous clinical studies:**

The clinical information contained in this Investigator's Brochure is based on the available clinical data, from the following completed or ongoing studies: GO39932, GO40987, WO42133, WO42312, BO41843, and GO42784.

Study GO39932

Study GO39932 is a Phase Ia/Ib, multicenter, open-label study evaluating the safety, pharmacokinetics, and anti-tumor activity of Giredestrant alone or in combination with palbociclib and/or LHRH agonist in patients with locally advanced or metastatic ER+breast cancer.

Study GO40987

Study GO40987 was a Phase I, open-label, multicenter, preoperative study to assess relative changes in Ki67 levels and to evaluate the pharmacodynamics, pharmacokinetics, safety, and biologic activity of Giredestrant in patients with Stage I–III operable ER-positive (HER2-negative) untreated breast cancer.

Study WO42133

Study WO42133 (coopERA) a Phase II randomized, open-label, two arm, multicenter study evaluated the efficacy, safety, and pharmacokinetics of Giredestrant versus anastrozole (for 14 days in the window-of opportunity phase) and Giredestrant plus palbociclib compared with anastrozole plus palbociclib (for 16 weeks in the neoadjuvant phase) in postmenopausal patients with untreated ER+ and HER2-negative EBC.

Study WO42312

Study WO42312 (acelERA Breast Cancer) is a Phase II, randomized, open-label multicenter study evaluating the efficacy and safety of Giredestrant compared with physician's choice of endocrine monotherapy (PCET [fulvestrant or an aromatase inhibitor]) in patients with ER+, HER2-negative MBC who have received one or two prior lines of systemic therapy in the locally advanced or metastatic setting.

Study BO41843

Study BO41843 (persevERA) is a Phase III randomized, double-blind placebo-controlled, multicenter study evaluating the efficacy and safety of Giredestrant combined with palbociclib compared with letrozole combined with palbociclib in patients with ER+, HER2-negative locally advanced (recurrent or progressed) or mBC. Approximately 978 patients are expected to be enrolled in the study.

Study GO42784

Study GO42784 (lidERA) is a Phase III, global, randomized, open-label, multicenter study evaluating the safety of Giredestrant compared with endocrine therapy of physician’s choice in participants ER+ and HER2− EBC.

I. Clinical Efficacy

- **Study GO39932**

  As of the CCOD (17 September 2021), 168/175 patients (96.0%) underwent at least one post-baseline tumor assessment, including patients who had been previously treated with Fulvestrant or CDK4/6 inhibitor, or those with baseline ER1 mutations

  Clinical benefit was observed across clinically relevant subgroups:

  - Among patients who had received prior Fulvestrant, 6/23 patients (26.1%) across all single agent cohorts, 3/8 patients (37.5%) in the 30 mg single-agent cohort, and 3/5 patients (60.0%) in the combination cohort with palbociclib (±LHRH agonist) achieved clinical benefit.
  - In those patients who received prior CDK4/6 inhibitors, 25/72 patients (34.7%) across all single-agent cohorts, 11/27 patients (40.7%) in the 30 mg single-agent cohort, and 4/5 patients (80.0%) in the combination cohort with palbociclib (±LHRH agonist) achieved

clinical benefit.

- In those patients who had a reported baseline ESR1 mutation, 26/52 patients (50.0%) across all single-agent cohorts, 13/21 patients (61.9%) at the 30 mg dose, and 18/18 patients (100%) in the combination cohort with palbociclib (±LHRH agonist) achieved clinical benefit.

- **Study WO42133**
  - The primary endpoint of relative changes in Ki67 scores from baseline to week 2 for Giredestrant versus anastrozole was met.
  - A greater rate of CCCA, defined as reduction of Ki67 to 2.7% or less, was achieved at week 2 with Giredestrant (20%) versus anastrozole (13%). ORR was evaluated after 16 weeks of treatment with endocrine therapy (Giredestrant or anastrozole) plus palbociclib. ORR was similar between the two arms (Giredestrant + palbociclib: 50% [95% CI: 40%, 60%]; anastrozole + palbociclib: 49% [95% CI: 39%, 59%]).

- **Study WO42312**

  Study WO42312 did not meet its primary endpoint of investigator-assessed PFS: Giredestrant showed a numerical improvement versus PCET in terms of PFS Hazard Ratio of 0.81 (95% CI: 0.60, 1.10), which was not statistically significant (p= 0.1757). Median PFS was similar between both arms, 5.55 months (95% CI: 4.93, 7.36) with Giredestrant and 5.36 months (95% CI%: 3.71, 5.55) with PCET. Treatment effect was overall consistent across most key subgroups; PFS benefit was more pronounced in the subset of patients with baseline ESR1 mutations (Hazard Ratio 0.60 [95% CI: 0.35, 1.03]). The OS data were still immature (<10% events). Numerical increases in other secondary endpoints were observed with Giredestrant, for both CBR (31.8% vs. 21.1%) and ORR (12.6% vs. 7.2%).

II. Clinical Safety

- **Study GO39932**

  No patients experienced dose-limiting toxicities and the MTD was not reached.

1. Adverse Events Attributed to Study Treatment:

- In the single-agent Giredestrant 30 mg cohort, of the AEs attributed to Giredestrant occurring in ≥5% patients included: fatigue, arthralgia, and nausea (14.6% each), dyspepsia (12.2%), dry mouth (9.8%), diarrhea, vomiting, and myalgia (7.3% each).
- The 64 patients treated with 100 mg of Giredestrant in combination with palbociclib (±LHRH agonist), AEs attributed to Giredestrant occurring in ≥5% patients were bradycardia (23.4%), diarrhea (7.8%), and photopsia, vision blurred, visual impairment, nausea, and neutropenia (6.3% each).

2. Grade 3-4 Adverse Events

- Across all single-agent cohorts (from 10 mg to 250 mg), Grade 3-4 AEs by PT that occurred in two or more patients regardless of causality were hypertension (2.7%), fatigue, diarrhea, and decreased appetite (1.8% each). One Grade 4 event (hypophosphatemia) assessed as unrelated was reported in a patient who received the 90 mg dose. Grade 3 AEs that were

reported as related by the investigator were ALT increased, AST increased, transaminase increased, diarrhea, fatigue, and hypertension (0.9% each).

- In the 30 mg single-agent cohort, there were no Grade 3 AEs by PT that occurred in ≥2 patients and there were no Grade 4 AEs reported. Grade 3 AE assessed as related by the investigator were ALT increased, AST, increased, and transaminase increased, each occurring in 1 (2.4%) patient each.
- In the combination cohort with palbociclib (±LHRH agonist), the proportion of patients with Grade 3−4 AEs was much higher in the combination cohort with palbociclib (±LHRH agonist) (73.4%) than in the single-agent cohorts (18.0%) and the 30 mg single-agent cohort (12.2%), mainly driven by hematological toxicities of palbociclib. Grade 3-4 AEs by PT that occurred in two or more patients regardless of causality were Grade 3: neutropenia (56.3%), thrombocytopenia.
- Grade 4 events of neutropenia were also reported in 7.8% of patients. Grade 3 AEs assessed as related to Giredestrant in this cohort were electrocardiogram QT prolonged and neutropenia (1.6% each). There were no Grade 4 AEs reported as related to Giredestrant in this cohort. (4.7%), and febrile neutropenia and white blood cell count decreased (3.1% each).

3. Deaths

- Three deaths were reported across all cohorts. No deaths were assessed as related to Giredestrant by the investigator.
- The fatal AEs were:
  - Duodenal ulcer perforation after starting a new line of therapy with paclitaxel (100 mg single-agent cohort).
  - Pleural effusion due to disease progression (30 mg single-agent cohort).
  - Breast cancer progression (combination cohort with palbociclib [±LHRH agonist]).

4. Serious Adverse Events

- SAEs were more frequent in the combination cohort with palbociclib (±LHRH agonist). SAEs were reported in 11 patients (9.9%) across all single-agent cohorts, 5 patients (12.2%) in the 30 mg single-agent cohort, and 13 patients (20.3%) in the combination cohort with palbociclib (±LHRH agonist).
- The only SAE reported in ≥2 patients was pleural effusion (1.8%). All SAEs were considered unrelated to Giredestrant by the investigator with the exception of Grade 3 fatigue (100 mg cohort;1 patient) and Grade 2 transient ischemic attack (30 mg single-agent cohort; 1 patient).
- In the combination cohort with palbociclib (±LHRH agonist), SAEs were reported in 13 patients (20.3%). The only SAE reported in ≥2 patients was neutropenia/neutrophil count decreased (6.3%). One SAE of Grade 3 electrocardiogram QT prolonged was considered related to Giredestrant by the investigator.

5. Adverse Events that Led to Withdrawal of Study Treatment

Of the 175 treated patients, three AEs leading to discontinuation of Giredestrant were reported in three patients. The AEs leading to discontinuation of Giredestrant were: • Fatal pleural effusion

due to disease progression (30 mg single-agent cohort). • Electrocardiogram QT prolonged and fatal breast cancer progression (combination cohort with palbociclib [±LHRH agonist]).

6. Cardiac Safety

Bradycardia

A total of 29/175 patients (16.6%) experienced bradycardia and these AEs were commonly reported (≥5%) across the single-agent cohorts, the 30 mg single-agent.

- The frequency of AEs of bradycardia reported in the combination cohort with Palbociclib (±LHRH agonist) was higher than that reported in the single-agent cohorts (28.1% vs. 9.9%), although bradycardia is not a known AE of palbociclib. ECG data showed similar HR changes in the single agent and combination cohorts.
- In the single-agent cohorts, 9.9% experienced bradycardia AEs. All were non-serious and Grade 1 with the exception of the following:
  1- One non-serious Grade 2 event reported as related to Giredestrant in one patient treated at 250 mg. The patient did not require treatment interruptions or dose reductions.
  2- One non-serious Grade 2 event of bradycardia in a patient treated at 30 mg, that was considered unrelated to Giredestrant. The event was attributed to concomitant digoxin and beta blockers for atrial fibrillation, and resolved once these were stopped.
- Within the 30 mg single-agent cohort, Grade 1 bradycardia AEs were reported in 2 patients with one Grade 2 case (as described above). The median time to onset was 594 days (range: 533−612) and the median duration was 29 days (range: 22−57) within the 30 mg single-agent cohort. Bradycardia AEs were also observed in the combination cohort with palbociclib (±LHRH agonist), occurring in 18 patients (28.1%) all of which were non-serious. All events were Grade 1 except one Grade 2 bradycardia (related to Giredestrant by the investigator). This Grade 2 event led to interruption of Giredestrant which was resumed at the same dose level without recurrence. Overall, 91.9% of bradycardia events were resolved or resolving at the time of the CCOD.

- **Study GO40987**

Safety data is available for 74 patients treated with Giredestrant at 10 mg-100 mg doses given once daily for approximately 14 days.

53 patients (71.6%) reported at least one AE, regardless of causality. This includes 12/17 patients (70.6%) in the 10 mg cohort, 27/40 patients (67.5%) in the 30 mg cohort, and 14/17 patients (82.4%) in the 100 mg cohort. Giredestrant was well tolerated at all dose levels: the majority of AEs reported were mild (Grade 1) or moderate (Grade 2) in maximum severity and there were no Grade ≥4 AEs reported in this study. No SAEs or Grade ≥3 AEs were assessed as related to Giredestrant by the investigator. No deaths were reported in the study and no new safety signal were detected.

1. Adverse Events Regardless of Attribution to Study Treatment

The most commonly reported AEs in ≥5% of all patients, following a 2-week course of Giredestrant were nausea (12.2%), fatigue (10.8%), dizziness (9.5%), hot flush, procedural

pain (8.1% each), headache, seroma, (6.8% each), arthralgia, asthenia and vomiting (5.4% each). The majority of the AEs were non-serious, mild or moderate in maximum severity and resolved without treatment or any clinical intervention.

2. **Adverse Events Attributed to Study Treatment**
   The majority of the related AEs were reported as recovered or recovering without the need for any treatment or clinical intervention and all AEs related to Giredestrant were considered non-serious Across all cohorts, the common AEs (≥2 patients) related to study drug were nausea (9.5%), fatigue (8.1%), dizziness (6.8%), hot flush (5.4%), arthralgia and asthenia (4.1% each), and diarrhea, dyspepsia, headache, photopsia, blurred vision, product dose omission in error, and product dose omission issue (2.7% each).

3. **Grade 3 Adverse Events**
   No Grade 4 or 5 AEs were reported in this study Overall, across all cohorts, five Grade 3 AEs occurred in 6.8% of all patients, all of which were considered unrelated by the investigator:
   - Breast abscess (10 mg)
   - Mastitis (30 mg)
   - Breast haematoma (30 mg)
   - Hypertension (30 mg)
   - Dizziness (100 mg)

4. **Serious Adverse Events**
   Of the 74 patients, (5.4%) experienced an SAE, all of which were considered unrelated by the investigator:
   - Breast abscess (10 mg)
   - Mastitis (30 mg)
   - Breast haematoma (30 mg)
   - Dizziness (100 mg)

5. **Cardiac Safety**
   Bradycardia
   1- As of the CCOD, a total of 2/74 patients (2.7%) receiving 30 mg Giredestrant experienced bradycardia AE. Both events were categorized as Grade 1 in maximum severity and non-serious events
   2- One bradycardia event was assessed as related to study drug by the investigator.
   3- No treatment or clinical intervention was required. The other bradycardia event was considered unrelated to study drug by the investigator and was considered related to concomitant medication (mebeverin and trazodone). No treatment or clinical intervention was required.

- **Study WO42133**

As of the CCOD (18 February 2022), safety data are available for 302 treated patients.

Overview of Adverse Events

Safety data is presented for patients treated with Giredestrant (n=150) and patients treated with physician's choice of ET (PCET: Fulvestrant or aromatase inhibitors) (n=152). Giredestrant treatment was well tolerated and considered to have comparable safety to PCET. Overall, 84.7% of Giredestrant patients experienced at least 1 AE compared to 71.1% in patients treated with PCET. AEs leading to dose modification or interruption occurred in 13.3% of Giredestrant patients and 8.6% of PCET patients. Few events led to treatment withdrawal, with 2 (1.3%) in the Giredestrant arm and 3 (2%) in the PCET arm. AEs reported with a ≥5% difference between arms are shown in the below table.

Adverse Events with a Difference of at Least 5% between Treatment Arms, Safety-Evaluable

Preferred Term	Giredestrant (n=150)	PCET (n=152)
Aspartate aminotransferase increased	22 (14.7%)	13 (8.6%)
Product dose omission in error	14 (9.3%)	0
Vomiting	13 (8.7%)	2 (1.3%)
Blood bilirubin increased	9 (6.0%)	1 (0.7%)
Product dose omission issue	9 (6.0%)	0

Adverse Events Regardless of Attribution to Study Treatment

In the Giredestrant arm (N= 150), AEs with an incidence of at least 5% include AST increase (14.7%), arthralgia (12%), ALT increase (11.3%), anemia (10%), nausea (10%), diarrhea (8.7%), vomiting (8.7%), fatigue (7.3%), headache (7.3%), and asthenia (6.7%); 6% of patients experienced blood bilirubin increase, bone pain, constipation, dizziness, and hypertension. 5.3% of patients experienced back pain, chest pain, and decreased appetite.

Serious Adverse Events

Serious AEs were reported in 9.3% of patients treated with Giredestrant and 7.9% in patients treated with PCET. SAEs considered related to treatment in 2.0% of Giredestrant treated patients and in 0.7% of PCET treated patients. SAEs reported in 2 or more patients treated with Giredestrant included ischemic stroke (3 patients), vomiting (2 patients), and cardiac failure (2 patients). SAEs reported in 2 or more patients in either arm are noted in the below table.

Table 16 Serious Adverse Events with a Difference of at Least 2% between Treatment Arms, Safety-Evaluable

Preferred Term	Giredestrant (n=150)	PCET (n=152)
COVID-19	0	3
Ischemic Stroke[1]	3	0
Vomiting	2	0
Seizures[2]	0	2
Cardiac Failure	2	0

1.Includes 2 ischemic stroke & 1 cerebral infarction 2.Includes seizures & epilepsy.

There were 2 (1.3%) AEs with a fatal outcome in the Giredestrant arm and 1 (0.7%) fatal AE in patients treated with PCET. The 2 AEs with fatal outcome in the Giredestrant arm were ischemic stroke, one of which was considered related and whose fatal outcome occurred after the CCOD. The fatal event in the PCET arm was an event of pulmonary embolism.

Grades 3−4 Adverse Events

Grade 3-4 AEs were reported in 17.3% of patients treated with Giredestrant and 11.8% of patients treated with PCET. Grade 3-4 events were considered related in 4.0% of Giredestrant treated patients and related in 2.6% of PCET treated patients. Grade 3-4 AEs reported in 3 or more Giredestrant treated patients regardless of relationship include aspartate aminotransferase increased (4 patients), blood bilirubin increased (3 patients), bone pain (3 patients), and hypertension (3 patients). Hypertension was also reported in 3 patients treated with PCET.

- **Study BO41843**

Overview of Adverse Events

Preliminary safety data for the study is provided only for overall patients and in an aggregate format and not by study treatment arm since treatment information is not known for this double blinded study. As of the CCOD of 31 January 2022, of the 685 patients that had received treatment, SAEs were reported in 61 patients (8.9%). Five patients (0.7%) experienced an SAE of Grade 1-2; 48 patients (7.0%) experienced an SAE of Grade 3−4 and 8 patients (1.2%) experienced a Grade 5 SAE. The most frequently reported SAE of any grade and reported in 3 or more patients includes dyspnea (0.7%), pleural effusion (0.6%), COVID-19 (0.4%), and blood creatinine increased (0.4%). As of the CCOD, 685 patients had received treatment. SAEs of Grade 3−4 intensity were reported in 48 patients. The most common SAEs of Grade 3−4 (occurring in ≥2 patients) included dyspnea (5 patients), pleural effusion (4 patients), pneumonia, dizziness, atrial fibrillation, hypomagnesaemia, febrile neutropenia, blood creatinine increased, and bone pain (2 patients each). There were 8 Grade 5 AEs out of 685 patients (1.2%), including: pulmonary embolism (1 patient), COVID-19 (2 patient), sepsis (1 patient), upper gastrointestinal hemorrhage (1 patient), multiple organ dysfunction syndrome (1 patient), death (1 patient) supraventricular tachycardia (1 patient). Selected AEs of interest were reported in 221 patients (32.3%) and the majority of events were Grade 1 or Grade 2 intensity (208 out of 685 patients [30.4%]). Overall 11 out of 685 patients (1.6%) had Grade 3 events of interest (nausea, vomiting, diarrhea, blood creatinine increased, acute

kidney injury, dizziness, electrocardiogram QT prolonged, and pulmonary embolism), 1 patient had a Grade 4 event of interest (blood creatinine increased), and 1 patient had a Grade 5 event of interest (pulmonary embolism).

- **Study GO42784**

Overview of Adverse Events

Preliminary safety data for the study is internally blinded and therefore is provided only for overall patients and in an aggregate format and not by study treatment arm. As of the CCOD of 31 January 2022, 106 patients had received Giredestrant treatment. One patient (0.9%) had a Grade 3 SAE of femur fracture. There were no SAEs of Grade ≥3 reported. As of the CCOD, of the 106 patients who received Giredestrant treatment, the AE (regardless of causality), occurring in 10% or more patients was hot flush. The majority of reported AEs, regardless of causality were Grade 1 or Grade 2 intensity (41 patients [38.7%]). One SAE of Grade 3 femur fracture was reported in a single patient. No deaths, treatment-related SAEs, serious AESIs, or Grade 4 events were reported.

Identified Risks and Adverse Drug Reactions

The classification of an AE as an ADR (identified risk) is based on the data available at the time of assessment. Data obtained at later dates (e.g., following unblinding of a Phase III trial) may refute the connection between an AE and Giredestrant, and lead to an ADR being subsequently reclassified as an AE, or confirm the association between an AE and Giredestrant, and cause the AE to be reclassified as an ADR. The frequency of risk is presented based on the interim results from the Phase Ia/Ib GO39932 study, final results from Phase I Study GO40987 (Window of Opportunity), and Phase II Study WO42312 (acelERA) and Study WO42133 (coopERA). The ADRs in the below table are listed by MedDRA PT term. The following categories of frequencies have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Summary of Identified Risks

Risk	Description of Risk
Arthralgia	Arthralgia was very commonly reported in patients treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Management of arthralgia should be according to local standard of care and institutional guidelines.
Bradycardia	Bradycardia was commonly reported in patients treated with giredestrant. All cases were non-serious and mild to moderate, with most cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Please refer to the study protocol for management guidelines.
Diarrhea	Diarrhea was very commonly reported in patients treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Please refer to the study protocol for management guidelines.
Dizziness	Dizziness was commonly reported in patients treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Dizziness should be managed according to institutional guidelines.
Headache	Headache was commonly reported in patients treated with giredestrant. Cases were non-serious and Grade 1 or Grade 2 in severity. Most headache events resolved without treatment.

Risk	Description of Risk
Hepatotoxicity	Events of AST increased and/or ALT were very commonly reported in patients treated with giredestrant. Events of blood bilirubin increased were commonly reported. The majority of events were Grade 1 or Grade 2, with few Grade 3 events. Overall, most events were non-serious and managed with either drug interruption or discontinuation of giredestrant, with treatment, or without any intervention. However, three serious cases were received: • One serious case of increased transaminases and bilirubin was received from Study WO42312 (acelERA). This occurred in the context of disease progression in a patient that was later found to have metastatic involvement of her gallbladder and common bile ducts. • One serious case of increased transaminases with normal bilirubin was received from Study CO42867 (MORPHEUS) in the giredestrant + ipatasertib arm. This patient had elevated transaminases at baseline, prior to dosing at Cycle 1 Day 1. The peak elevation of transaminases approximately 2.5-fold higher than her baseline values (Grade 1 per CTCAE v5). • One serious case of increased transaminases and bilirubin was received from Study GP44001. This patient had LFT results within normal limits at baseline but developed AST of 1164 U/L and 2162 U/L and a total bilirubin of 2.0 mg/dL approximately 7 days after her first dose of giredestrant, resulting in hospitalization. She was discharged the following day with improvements in ALT and AST (636 and 195 U/L, respectively). Transaminases continued to improve in the following days. All three serious cases were assessed as related to giredestrant by the reporting investigator.
Hot flush	Hot flush was very commonly reported in patients treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum severity. In Study WO42133 (coopERA), 1 Grade 3 event was reported in the giredestrant + palbociclib arm. The event did not lead to study treatment discontinuation or dose interruption or reduction of palbociclib. Hot flush should be managed according to institutional guidelines.
Fatigue	Fatigue was very commonly reported in patients treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum severity. The vast majority of cases resolved without intervention or interruption of study drug. Fatigue should be managed according to institutional guidelines.

Risk	Description of Risk
Musculoskeletal pain	Musculoskeletal pain was very commonly reported in patients treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum severity. The vast majority of cases resolved without intervention or interruption of study drug. Management of musculoskeletal pain should be according to institutional guidelines.
Nausea	Nausea was very commonly reported in patients treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum severity. The vast majority of cases resolved without intervention or interruption of study drug. Please refer to the study protocol for management guidelines.
Vomiting	Vomiting was commonly reported in patients treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum severity. The vast majority of cases resolved without intervention or interruption of study drug. Please refer to the study protocol for management guidelines.

Potential Risks

On the basis of clinical and nonclinical toxicology findings for Giredestrant and known toxicities associated with other drugs in the ER antagonist class, the potential risks of Giredestrant are described below. These risks are not considered ADRs.

- **Renal dysfunction**

  Dose-dependent effects on the kidneys were observed in repeat-dose studies in both rats and monkeys given Giredestrant. In Study GO39932 (N=175), as of CCOD, 5.1% of patients experienced AEs that might be suggestive of renal toxicity. All AEs were non-serious and Grade 1 in maximum severity, with the exception of 3 patients who experienced Grade 2 AEs. Of the total number of these AEs, 11.1% required treatment, and 22.2% required a dose interruption to Giredestrant; 85.7% of events had resolved. The events were considered related to Giredestrant in 21.4% of patients experiencing a AE suggestive of renal dysfunction. There were no patients in study GO40987 that experienced any AEs suggestive of renal dysfunction.

- **Venous Thromboembolic Events**

  There were no patients in study GO40987 that experienced any AEs suggestive of venous thromboembolic events. In Study GO39932 (N=175), as of CCOD, 1.1% of patients experienced thromboembolic events. In patients treated with the 100 mg dose (n=55), one patient (1.8%) experienced a serious Grade 3 pulmonary embolism, considered unrelated to Giredestrant. Treatment was interrupted for this patient and the event resolved. All other thromboembolic events were non-serious. In patients treated with the combination cohort with palbociclib (±LHRH agonist) (n=64), a Grade 2 event of deep vein thrombosis reported in one (1.6%) patient. This event was considered to be unrelated to Giredestrant. Treatment with Giredestrant was interrupted and the event resolved.

- **Changes in Female Reproductive Organs and Other Menopausal symptoms**

  The reproductive system or breast: vulvovaginal dryness, vaginal discharge, dyspareunia, vulvovaginal pruritus, and atrophic vulvovaginitis. No patient required any changes to dosing due to AE. The majority of patients did not receive treatment for the AEs and 5/13 AEs had resolved or were resolving by the CCOD.

- **Male/Female Infertility**

  The effects of Giredestrant on fertility in humans have not been studied. Perturbation and arrest of the estrus cycle was observed microscopically in both rats and monkeys. This was evidence of a return to estrus cycling following a 16-week recovery period. While these findings remain incompletely explained, any patients with concerns for future fertility should be made aware of this potential issue prior to coming onto any study. Their concerns, including fertility preservation, should be discussed prior to coming onto any study with Giredestrant.

Special Patient Populations

Pregnancy

No clinical studies assessing the reproductive and developmental toxicity of Giredestrant have been conducted to date. It is not known whether Giredestrant can cross the placenta or cause harm to the fetus when administered to pregnant women or whether it affects reproductive capacity. However, based on the anti-estrogenic pharmacological activity of Giredestrant, administration during pregnancy is expected to have an adverse effect on the developing fetus. Microscopic evidence of disruption of the estrus cycle was present in both rats and cynomolgus monkeys administered Giredestrant with evidence of reversibility following a 16-week recovery period.

Nursing Mothers

It is not known whether Giredestrant is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for SADRs in nursing infants, Giredestrant should not be administered to nursing mothers.

Children

Safety and effectiveness in pediatric patients under the age of 18 years have not been established; therefore, Giredestrant should not be administered to this patient population.

Geriatric Patients

Clinical studies of Giredestrant include patients >65 years old. In Study GO40987, 41.9% of patients were > 65 years old across all treatment arms. In Study WO42133, 38.9% of patients were >65 years old across all treatment arms. In Study GO39932, 26.9% of patients were>65 years old across all treatment arms. In Study WO42312, 32.7% of patients were >65 years old across all treatment arms.

Concomitant Use with Other Medications

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, beta blockers and calcium channel antagonists.

- **Protocol:** A Phase 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

Phase: **I** ☐ **II** ☐ **III** ■ **IV** ☐

Objective(s):

This study will evaluate the efficacy and safety of Giredestrant in combination with Phesgo compared with Phesgo after induction therapy with Phesgo + Taxane in participants with previously untreated HER2-positive, ER-positive ABC (metastatic or locally-advanced disease not amenable to curative treatment). The primary comparison of interest is the hazard ratio (HR) of PFS. The primary trial objective is to demonstrate superiority of the Giredestrant plus Phesgo arm over the Phesgo arm.

Primary and Secondary Objectives and Endpoints:

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of Phesgo plus giredestrant compared with Phesgo	• PFS, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of Phesgo plus giredestrant compared with Phesgo	• OS, defined as the time from randomization to death from any cause • ORR (following randomization), defined as the proportion of participants with a CR or PR on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1 • DOR (following randomization), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • CBR (following randomization), defined as the proportion of participants with SD for ≥24 weeks or a CR or PR, as determined by the investigator according to RECIST v1.1 • Mean and mean changes from baseline score in function (role, physical) and HRQoL by cycle and between treatment arms as assessed through the use of the Functional and GHS/QoL scales of the EORTC QLQ-C30
• To evaluate the safety of Phesgo plus giredestrant compared with Phesgo	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Change from baseline in targeted clinical laboratory test results

CBR=clinical benefit rate; CR=complete response; CTCAE = Common Terminology Criteria for Adverse Events; DOR= duration of response; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire; GHS/QoL=global health status/ quality of life; HRQol=health-related quality of life; PFS= progression-free survival; PR=partial response; NCI = National Cancer Institute; ORR=objective response rate; OS=overall survival; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SD=stable disease.

Rationale:

The purpose of this study is to assess the efficacy and safety of Giredestrant, a novel oral selective estrogen receptor degrader (SERD) in combination with Phesgo (Pertuzumab, Trastuzumab, and rHuPH20 injection, for SC use) in participants with previously untreated, locally-advanced unresectable, or metastatic, estrogen receptor (ER)-positive, HER2-positive breast cancer (BC), following four to six cycles of induction therapy with Phesgo +Taxane (i.e., docetaxel or paclitaxel, as per the standard of care).

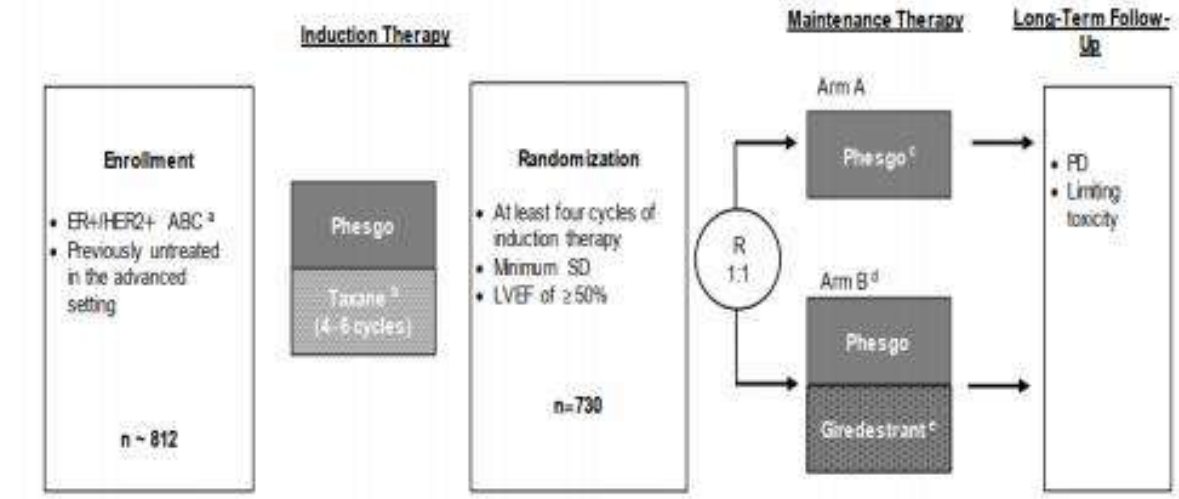
Design:

This Phase III, randomized, two-arm, open-label, multicenter study will evaluate the efficacy and safety of Phesgo plus Giredestrant compared with Phesgo after induction with Phesgo + Taxane in participants with HER2-positive, ER-positive ABC (metastatic or locally-advanced disease not amenable to curative treatment) who have not previously received a systemic non-hormonal anti-cancer therapy in the advanced setting. Study treatment is comprised of two phases: induction therapy followed by study maintenance therapy.

In this protocol, "induction therapy" refers to treatment with Phesgo + Taxane and "study maintenance treatment" refers to Phesgo plus Giredestrant or Phesgo.
Approximately 812 participants will be enrolled into the induction therapy phase during which they will receive four to six cycles of Phesgo in combination with a Taxane (i.e., docetaxel or paclitaxel, as per the standard of care. At the investigator's discretion, participants who tolerate six cycles of induction therapy well and do not experience PD may be given up to two additional cycles: up to a maximum of eight cycles as per the standard of care. Participants who have received one or two cycles of Phesgo (or Pertuzumab IV with Trastuzumab SC or PH IV) with docetaxel or paclitaxel prior to enrollment are eligible and these additional cycles will count towards eligibility for the maintenance phase.

Following the induction therapy phase, eligible participants will be randomized into the maintenance therapy phase during which they will receive Phesgo plus Giredestrant or Phesgo in 21-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end, whichever occurs first.

Figure 1 Study Schema



ABC=advanced breast cancer; AI= aromatase inhibitor; CR=complete response; ER=estrogen receptor; ET= endocrine therapy; LHRHa=luteinizing hormone–releasing hormone agonists; LVEF= left ventricular ejection fraction; R=randomized; PD=progressive disease; SD=stable disease

Breast cancer is the most common cancer among women. In 2020, an estimated 2.26 million cases were diagnosed globally and approximately 685,000 deaths were attributed to this disease (Sung et al. 2021). Approximately 15%-20% of patients with primary invasive BCs overexpress HER2. Prior to the availability of HER2-directed therapies, these patients had worse prognoses, including a greater risk of relapse and shortened survival time, compared with patients with HER2-negative BC. The pivotal CLEOPATRA trial (Study WO20698) demonstrated the survival advantages and manageable toxicity profile of a dual HER2-blockade with Herceptin® (trastuzumab) and Perjeta® (Pertuzumab) combined with the cytotoxic agent docetaxel. Beginning in 2012, this regimen became widely accepted as the first-line treatment for patients diagnosed with HER2-positve advanced breast cancer (ABC). ER expression in HER2-positive BC implies a rather distinct biology compared to that of ER-negative, HER2-positive BC: patients diagnosed with ER-positive, HER2-positive BC have tumors that are less

proliferative, have lower HER2 gene amplification, and lower response rates to chemotherapy with anti-HER2 therapies). A bi-directional cross-talk between the HER-family and ER has been fully characterized at cellular level, whereby suppression of either receptor alone is associated with upregulation of the other, ultimately leading to resistance to therapy. PERTAIN (Study MO27775) also demonstrated the beneficial effect of a dual HER2 blockade with ET; an improvement in progression-free survival (PFS) alongside good tolerability was observed with the addition of Pertuzumab to trastuzumab (PH) plus an aromatase inhibitor (AI), over trastuzumab plus AI alone.

Roche is developing Giredestrant, a potent, orally bioavailable ER-α antagonist and inducer of ER-α degradation that competes with estrogens for binding to the ER with low nanomolar potency. It is being developed as a new ET for the treatment of patients with ER-positive ABC, as well as early breast cancer (EBC) (Liang et al. 2021). Giredestrant antagonizes the effects of estrogens via competitive binding to the ligand-binding domain (LBD) of both wild-type and mutant ER with nanomolar potency. In addition to its direct antagonist properties, the mechanism of action of Giredestrant includes reducing levels of ER protein through proteasome-mediated degradation. Degradation of ER is hypothesized to enable full suppression of ER signaling, which is not achieved by first-generation ER therapeutics such as tamoxifen that display partial agonism. Giredestrant potently inhibits the proliferation of multiple ER-positive BC cell lines in vitro, including cells engineered to express clinically relevant mutations in ER. Although Giredestrant has not been studied in patients with ER-positive, HER2-positive BC, nor in combination with PH, in three different cell lines that co-express ER and HER2 (UACC-812, HCC1419, and ZR-75-30), the combination of Giredestrant with PH had better antiproliferative activity than Giredestrant or PH given alone (internal Roche data). Additionally, preliminary studies suggest that ER-positive, HER2-positive patients with ABC might also benefit from an optimized ET in combination with PH.

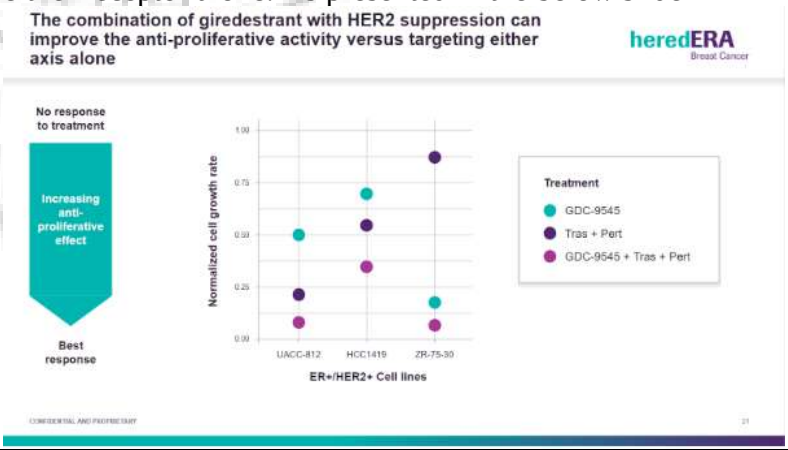
Benefit-Risk Assessment:

In a Phase I study (Study GO39932), Giredestrant monotherapy showed promising signs of clinical activity at the recommended phase 2 dose of 30 mg daily and was safe in patients with previously treated ER-positive, HER2-negative ABC. In the Phase II, randomized coopERA study (study WO42133), neoadjuvant Giredestrant was demonstrated to be superior to anastrozole to achieve Ki67 suppression and complete cell cycle arrest in patients with ER-positive, HER2-negative EBC. Patients with ER-positive, HER2-positive BC have been shown in exploratory analyses of a phase 3 trial to benefit from enhanced ET partners with dual HER2 blockade. Because the first-in-class SERD, Fulvestrant, has been shown superior to AI in first line ER-positive, HER2-negative ABC patients, Giredestrant, which fully degrades and suppresses ER with higher potency than Fulvestrant, may have enhanced efficacy in ER-positive, HER2-positive ABC compared with available maintenance therapies.

Overall, the identified risks of Giredestrant include gastrointestinal toxicity (nausea, vomiting, diarrhea), arthralgia, musculoskeletal pain, dizziness, bradycardia, hepatotoxicity, headache, hot flushes, and fatigue. The potential risks of Giredestrant include venous thromboembolism, renal dysfunction, menopausal symptoms, infertility and embryofetal toxicity. Most importantly, there are no expected major overlapping toxicities between Giredestrant and Phesgo, with previous experience of different ET combined with Trastuzumab ± Pertuzumab showing the safety and feasibility of such an approach. Given the therapeutic opportunity presented by ER co-expression, augmenting maintenance therapy (i.e., following chemotherapy discontinuation) with an optimized ET backbone including Giredestrant is a next step in patients with ER-positive, HER2-positive ABC to potentially improve their outcomes without jeopardizing the safety profile of maintenance PH.

Taking into account Giredestrant efficacy data in patients with ER-positive, HER2-negative BC, the safety profiles for Phesgo and Giredestrant, the expected synergy of such a combination, the unmet medical need of better survival outcomes for patients with ER-positive, HER2-positive ABC, and the risk mitigation measures for the study, the benefit-risk ratio is expected to be acceptable for Phesgo plus Giredestrant following four to six cycles of a Phesgo+Taxane for patients with previously untreated, locally-advanced unresectable or metastatic ER-positive/HER2-postitive BC.

- **Questions & Answers:**

1. Referring to the protocol design "Arm A (Phesgo: control arm): participants will receive Phesgo subcutaneously every 3 weeks (Q3W). Optional concomitant ET of investigator's choice is allowed based on the standard of care." Kindly be informed that for Egypt Sites, for participants who will be enrolled to Arm A (Phesgo; Control) concomitant ET of Investigator's Choice is a must (not optional) according to the local standard of care .	Kindly note that after our conversation with the PIs, it was clearly stated that the ET is a standard of care for patients enrolled in Arm A
2. Referring to the statement that "The combination of Giredestrant with PH had better antiproliferative activity than Giredestrant or PH given alone (internal Roche data)", clarification is required regarding the internal Roche data and thorough submission of detailed information is necessary.	HER2+ ER+ cell lines were exposed to either giredestrant alone, Trastuzumab/Pertuzumab or giredestrant + Trastuzumab/Pertuzumab. What was observed using a 7 day viability assay was that the best anti-proliferative effect that was observed was with the combination of giredestrant + Trastuzumab/Pertuzumab that permitted dual blockade of both HER2 and ER signalling, compared to blockade or either receptor alone. As presented in the below slide 
3. As mentioned in protocol section 4.2.4. "Patients who received six cycles derived similar survival benefits with the addition of pertuzumab to trastuzumab, as	Kindly note as per the protocol section 4.1.1 & 4.1.2 it is allowed to have up to 8 cycles at the PI investigator's discretion, participants who tolerate six cycles of induction therapy well and do not experience PD may be given up to two additional cycles: up to a maximum of eight cycles as

	compared with those patients who received more than six cycles of docetaxel, with fewer patients discontinuing docetaxel due to adverse events and intercurrent illness for patients receiving six cycles (13.7%) relative to patients receiving more than six cycles (37.7%) (Miles et al. 2017)", Therefore, more clarification is required for allowing up to 8 cycles of induction therapy	per the standard of care of the institution . Also it is mentioned in section 4.2.4, in order to maximize the clinical benefits during the induction therapy phase, participants who are tolerating the induction therapy may be given up to an additional two cycles of the same taxane +Phesgo after completing six cycles of induction therapy prior to randomization, for a total of up to eight cycles, according to investigator's discretion.

- **Abbreviation:**

ABC: Advance Breast Cancer
ADR: Adverse Drug Reaction
AE: Adverse Event
AI: Aromatase Inhibitor
AUC: Area under the Concentration-Time Curve
BC: Breast Cancer
CBR: Clinical Benefit Rate
CCCA: Complete Cell Cycle Arrest
CCOD: Clinical Cutoff Date
CDK: Cyclin-Dependent Kinase
C_{max}: Maximum Plasma Concentration
E2: Estradiol
EBC: Early Breast Cancer
EC_{50}: Half-Maximal Effective Concentration
ECG: Electrocardiogram
EE: Ethinylestradiol
ER: Estrogen Receptor
FOB: Functional Observation Battery
GD: Gestation Days
GLP: Good Laboratory Practice
HER2: Human Epidermal Growth Factor Receptor 2
HR: Hazard Ratio
HR: Heart Rate
IB: Investigator's Brochure
IC_{50}: 50% inhibitory concentration
IC_{90}: 90% inhibitory concentration
ICF: Informed Consent Form
IRB: Institutional Review Board
LBD: Ligand-Binding Domain
LHRH: Luteinizing Hormone-Releasing Hormone

mBC: Metastatic Breast Cancer
MCF7: Michigan Cancer Foundation 7
MTD: Maximum Tolerated Dose
NOEL: No-Observed-Effect Level
ORR: Overall Response Rate
OS: Overall Survival
PCET: Physician's Choice of Endocrine Monotherapy
PD: Progressive Disease
PFS: Progression Free Survival
PH: Perjeta and Herceptin IV/SC
PLD: Phospholipidosis
PO: By Mouth
PT: Preferred Term
QD: Once Daily
SAE: Serious Adverse Event
SC: Subcutaneous
SERD: Selective Estrogen Receptor Degrader
TGI: Tumor Growth Inhibition
TK: Toxicokinetic
WT: Wild-Type

Prepared by Unit manager:
Name: Dalia Kamal
Signature:
Date: 05-06-2024

Protocols and studies Follow up Administration Manager:
Name: Rania Shosha
Signature:
Date: 05-06-2024