PROTOCOL

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 NUMBER:	WO43571
STUDY NAME*:*	heredERA
VERSION NUMBER:	3
TEST COMPOUNDS:	Phesgo (pertuzumab, trastuzumab, and rHuPH20) (RO7198574) Giredestrant (RO7197597)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 131009 EU Trial Number: 2022-500014-26-00 NCT Number: NCT05296798
SPONSOR NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
3	See electronic date stamp on the final page of this document.
2	19 May 2022
1	2 February 2022

PROTOCOL AMENDMENT, VERSION 3

RATIONALE

Protocol WO43571 has been amended primarily to align with the Giredestrant Investigator's Brochure and the Investigator's Brochure addendum to Version 6. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The following changes have been made to the schedule of activities (Section 1.3):
  - The timing of tumor assessments has been updated to clarify that assessment timing should be based on the date of administration of the first induction treatment (on or off study, whichever is earlier) and not on the date of enrollment (Table 1 and Section 8.1.1).
  - The timing of echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) assessments has been updated to clarify that it includes any off-study induction cycles (Table 1).
  - It has been clarified that postmenopausal patients only need to have follicle-stimulating hormone (FSH) and estradiol measured at screening to confirm their postmenopausal status (Table 1 and Table A6−1).
  - It has been clarified that men and pre- and perimenopausal women may be required to receive luteinizing hormone-releasing hormone agonist (LHRHa) if an optional endocrine therapy (ET) is chosen or if the patient is randomized to Arm B (Table 1).
  - A time window for pregnancy testing in the induction and maintenance phases has been added to allow more flexibility and to enable the testing to be performed by a mobile nurse (Table 1, footnote "k" and Table A6-1).
  - It has been clarified that anti-drug antibody (ADA) and pharmacokinetic (PK) samples should be taken at the treatment discontinuation visit. The pharmacokinetics and ADA sample collections during the follow up period (months 3, 12, and 24) have been removed from Table 5 due to well characterized PK and ADA profiles for trastuzumab, pertuzumab (within Phesgo) in previous studies and the aim to decrease the burden on blood draw from patients during the follow-up period (Table 1 and Table 5).
  - The required visit schedule has been corrected for a few patient-reported outcome assessments (Table 2 and Table 3).
  - The collection of PK and ADA samples for pertuzumab, trastuzumab, and rHuPH20 has been removed in Arm A in the maintenance phase, as the pharmacokinetic profile and immunogenicity responses in the control arm are expected to follow responses seen in historical ADA data (Table 5 and Section 9.3).
- Identified and potential risks have been updated to align with the Giredestrant Investigator's Brochure, Version 6 (Sections 2.3 and A3-2.2).

- The participant-reported outcome has been changed to patient-reported outcome throughout the protocol (Table 6, Sections 4.1.1, 8.1.2.4, 9.4.7.5, A2–7.13, A5–1).
- The exploratory objectives have been updated to clarify that certain analyses will be conducted when Phesgo and giredestrant are given in combination (Section 3, Table 6).
- The disease status stratification factor has been updated to clarify what is considered a visceral metastases (i.e., brain/lung/liver) (Sections 4.1.3 and 4.2.7).
- The rationale for pharmacokinetic sample collection schedule was added to further clarify the sampling schedule (Section 4.2.9).
- The inclusion criteria have been updated to define pre-, peri-, and postmenopausal status and to clarify that the required ANC values do not need to be achieved without granulocyte colony-stimulating factor support (Section 5.1).
- The exclusion criteria have been updated as follows (Section 5.2):
  - It has been clarified that patients previously treated in the early setting with single-agent trastuzumab are eligible for the study.
  - Information regarding viral hepatitis has been further clarified to more clearly define active infection.
  - The exceptions for exclusion of individuals who are HIV-positive have been clarified regarding treatment with anti-retroviral therapy duration and CD4 count.
- The criteria for re-screening after screen failure have been updated to clarify the need to repeat assessments (Section 5.4).
- Regarding missed Phesgo doses, it has been clarified that if the time between doses is ≥ 6 weeks but ≤ 9 weeks, a reloading dose of Phesgo should be given, while if the time between doses is > 9 weeks, the patient should be discontinued from study treatment (Section 6.1.1).
- It has been clarified that if using optional ET, switching from one ET to another due to toxicity is not allowed (Section 6.1.4).
- Assessment of menopausal status has been added upon withdrawal of LHRHa to confirm postmenopausal status (Section 6.1.5).
- A correction has been made that study investigational medicinal products (IMPs) may continue to be provided to participants after the end of the study, under certain circumstances (Section 6.6).
- The following CYP3A changes were made to align with the Giredestrant Investigator's Brochure and the Investigator's Brochure addendum to Version 6:
  - The previous treatment with strong CYP3A inhibitors or inducers has been added as an exclusion criterion. In addition, consumption of grapefruit, grapefruit juice, grapefruit supplements, or Seville oranges (potent CYP3A inhibitors) within 3 days prior to initiation of giredestrant treatment in Arm B is now prohibited (Sections 5.1.1, 5.2, and 5.3.1).

  - The prohibited therapy list has been updated to include instruction to avoid concomitant use of strong CYP3A inhibitors or inducers with giredestrant (Section 6.8.2).

- A recommendation has been added to advise investigators to consider alternatives to using moderate CYP3A inducers concomitantly with giredestrant or limit them to short-term use (Section 6.8.4.3).
- The prohibited therapy list and guidelines for febrile neutropenia management have been corrected to remove the prohibition of prophylactic use of hematopoietic growth factors (Section 6.8.2 and A3-3.1.4).
- Regarding radiographic assessments at baseline, examples of types of bone scans or other institutional standard bone imaging have been added (Section 8.1.1.1).
- It has been clarified that the time period up to the primary analysis is based on first patient randomized rather than on first patient enrolled (Section 9.2).
- To align with the Sponsor's process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access if required by local regulations (Section A1–5).
- The Sponsor record retention policy has been clarified (Section A1–6).
- The signs and symptoms experienced due to lack of efficacy or unexpected worsening of disease have been removed, as they do not need to be specifically reported as adverse events and such reporting is not a requirement of the study (Sections A2–1 and A2–7.10).
- Bradycardia, hepatotoxicity, and headache have been confirmed as identified risks associated with giredestrant use per the Giredestrant Investigator's Brochure. Version 6. Therefore, bradycardia and hepatotoxicity have been moved from the potential risk section to the identified risk section and headache has been added to the identified risk section (Section A3–2.1).
- The drug-drug Interaction section for giredestrant has been removed (previous Section A3–2.2.8) as the new concomitant therapy guidance for giredestrant has been added in the prohibited therapy and cautionary therapy sections.
- QT management guidelines have been removed based on available data showing that giredestrant has a low risk of QT prolongation at the clinical and supratherapeutic dose (Sections A3–3.2.3 and A3–3.2.4).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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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**
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SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form *to your local monitor.*

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

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**
REGULATORY AGENCY IDENTIFIER NUMBERS	IND Number: 131009 EU Trial Number: 2022-500014-26-00 NCT Number: NCT05296798

STUDY 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). Despite advances in early diagnosis and curative multimodality treatments, some patients may still experience a metastatic recurrence or present with “de novo” metastatic breast cancer (MBC). There continues to be a need for treatments with better benefit–risk profiles that prolong progression free survival (PFS) and other survival endpoints of patients with ER-positive, HER2-positive advanced breast cancer (ABC).

OBJECTIVES AND ENDPOINTS

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.

In this protocol, “induction therapy” refers to treatment with Phesgo + taxane and "study maintenance treatment" refers to Phesgo plus giredestrant or Phesgo.

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020).

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 = ealth-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.

OVERALL DESIGN *AND STUDY POPULATION*

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 advanced breast cancer (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. Approximately 812 participants will be enrolled into the induction therapy phase, and approximately 730 participants will be randomized in the maintenance therapy phase. Participants who are still in the induction therapy phase after this target is reached will be also be allowed to enter the maintenance therapy phase, if they are deemed eligible by the investigator.

STUDY TREATMENT

During the induction therapy phase, participants 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 progressive disease (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 trastuzumab SC with pertuzumab IV, 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.

Participants will be followed for safety for 28 days after the final dose of study treatment, including a treatment discontinuation visit at 28 days (±3 days) after the final dose of Phesgo. Thereafter, information on survival and new anti-cancer therapy will be collected every 3 months until death (unless the participant withdraws consent or the Sponsor terminates the study). The survival follow-up period for participants remaining in the study will conclude at the time of the final overall survival (OS) analysis.

A study schema is provided in Section 1.2 (see Figure 1). Refer to Section 1.3 for a schedule of activities (Table 1), schedule of PRO assessments (Table 2, Table 3, and Table 4) and a sample collection schedule (Table 5).

DURATION OF STUDY PARTICIPATION

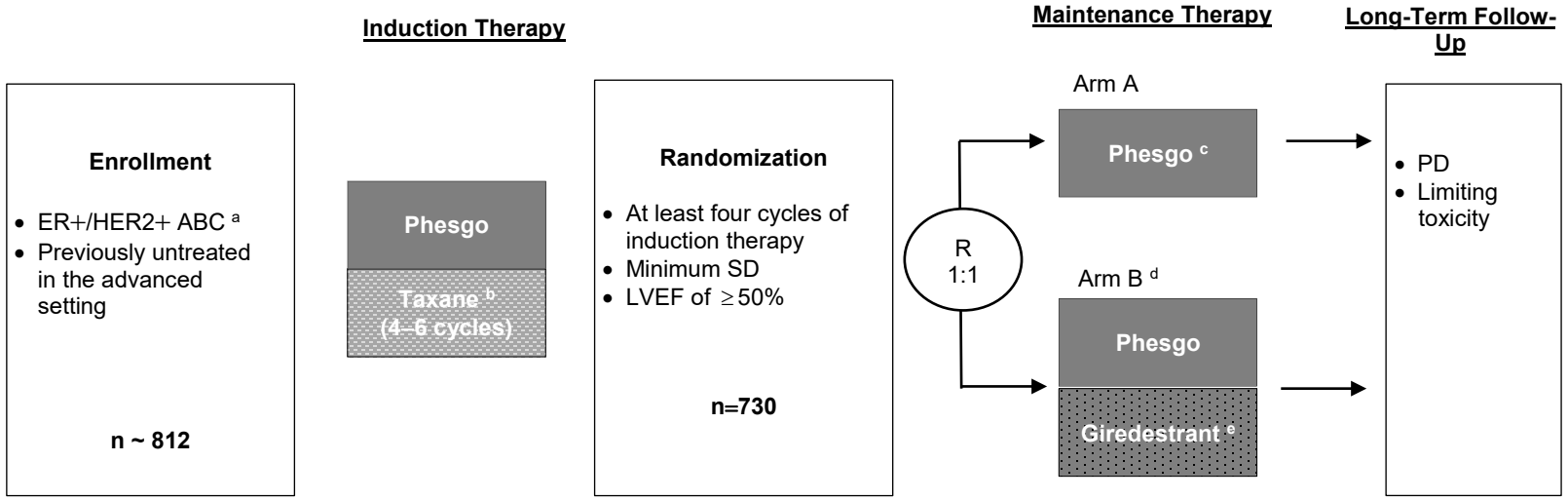
The total duration of study participation for each individual is expected to range from 1 day to more *than* 86 months.

INDEPENDENT DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (iDMC) is being used and will evaluate unblinded safety data on a regular basis during the study, including a review of safety data after 25 participants in Arm B complete two cycles of maintenance treatment, in order to ensure the combinability of Phesgo and giredestrant.

1.2 STUDY SCHEMA

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

[a] HER2 expression will be assessed centrally prior to a participant enrolling in the study.

[b] Docetaxel or paclitaxel at the investigator's discretion as per the standard of care. Participants must receive a minimum of four complete cycles of induction therapy (including cycles received prior to study enrollment, if applicable). At the investigator's discretion, participants who tolerate six induction therapy cycles well and do not experience PD may be given up to two additional cycles, up to a maximum of eight cycles.

[c] Optional ET of investigator's choice is allowed based on the standard of care (ET can include an AI or tamoxifen ± LHRHa or gonadal ablation). The decision to include or exclude this option must be made prior to randomization and documented in the source notes and recorded in the IxRS.

[d] The iDMC will review safety data after 25 participants in Arm B complete two cycles of treatment.

[e] Pre- and perimenopausal women, and all men will receive a LHRHa every 28 days and up to 28 days prior to the first giredestrant dose. Alternatively, women who are pre-or perimenopausal can be treated with bilateral oophorectomy.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

		Screening [a]		Induction Therapy Cycles [b] (21-day cycle)	Maintenance Therapy Cycles [c] (21-day cycle)	Treatment Discontinuation	Long-Term Follow-Up (Q3M) [d]
Day (Window)	Protocol Reference	–28 to enrollment	–7 to enrollment	1 (± 3 days)	1 (± 3 days)	28 days after final dose of Phesgo (± 3 days)	(± 15 days)
Informed consent	8	x [e]					
Demographics	8	x					
Medical history and baseline conditions	8	x					
Tumor tissue submission for prospective HER2 status assessment (central lab)	Table 6 8.7	x (may be performed outside of the 28-day screening window)					
Tumor assessment [f]	8.1.1	x		x 9 weeks after *first induction therapy (on or off study)*, then Q12W for 36 months, Q18W thereafter. A window of ±7 days is allowed		x [f]	
Vital signs	8.2.2	x		x	x [h]	x	
Weight		x				x	
Height		x					
Complete physical examination	8.2.1	x				x	

Table 1 Schedule of Activities (cont.)

		Screening [a]		Induction Therapy Cycles [b] (21-day cycle)	Maintenance Therapy Cycles [c] (21-day cycle)	Treatment Discontinuation	Long-Term Follow-Up (Q3M) [d]
Day (Window)	Protocol Reference	–28 to enrollment	–7 to enrollment	1 (± 3 days)	1 (± 3 days)	28 days after final dose of Phesgo (± 3 days)	(± 15 days)
Limited physical examination	8.2.1			x	x [h]		
12-Lead ECG	8.2.4.2	x			Day 1 of Cycle 1, and then at the same cycles as ECHO/ MUGA scan thereafter	x	
ECHO or MUGA scan [i]	8.2.4	x		X Every four cycles, *including any off study induction cycles*		x	x
ECOG Performance Status	8.2.3	x		x	x [h]	x	
Hematology [j]	Table A6-1		x	x [g]	Day 1 of Cycle 1 and Cycle 2, and on Day 1 of every four cycles thereafter [g]	x	
Chemistry [j]	Table A6-1		x	x [g]	Day 1 of Cycle 1 and Cycle 2, and on Day 1 of every four cycles thereafter [g]	x	
Coagulation: INR (or PT) and aPTT (or PTT) *j*	Table A6-1		x	As clinically indicated [g]			
Pregnancy test [k]	Table A6-1	x		x [g]		x	x [k]

Table 1 Schedule of Activities (cont.)

		Screening [a]		Induction Therapy Cycles [b] (21-day cycle)	Maintenance Therapy Cycles [c] (21-day cycle)	Treatment Discontinuation	Long-Term Follow-Up (Q3M) [d]
Day (Window)	Protocol Reference	–28 to enrollment	–7 to enrollment	1 (± 3 days)	1 (± 3 days)	28 days after final dose of Phesgo (± 3 days)	(± 15 days)
Urinalysis [j]	Table A6-1		x	As clinically indicated [g]			
• FSH and estradiol (*P*re- and perimenopausal participants, female participants aged <60 years, and participants receiving LHRHa. *For female postmenopausal participants aged <60 years, applicable only at screening to confirm postmenopausal status as defined in Section 5.1*)	Table A6-1	x			Day 1 of each cycle for 4 cycles and then every 4 cycles thereafter [g]	x	
Phesgo administration	6.1.1			x	x [h, l]		
Taxane administration	6.1.3			x			
Giredestrant administration	6.1.2				QD Days 1–21 of each cycle (Arm B) [l]		
Medication Diary (paper)					Complete when medication is taken at home or at clinic visit		

Table 1 Schedule of Activities (cont.)

		Screening [a]		Induction Therapy Cycles [b] (21-day cycle)	Maintenance Therapy Cycles [c] (21-day cycle)	Treatment Discontinuation	Long-Term Follow-Up (Q3M) [d]
Day (Window)	Protocol Reference	–28 to enrollment	–7 to enrollment	1 (± 3 days)	1 (± 3 days)	28 days after final dose of Phesgo (± 3 days)	(± 15 days)
Optional endocrine therapy	6.1.4				Administered to applicable participants (Arm A)		
LHRHa administration *(for pre-/*perimenopausal women and all men in *Arm B or in Arm A using* optional ET) [m]	6.1.5				Administered to applicable participants every 28 days [h]		
EORTC QLQ-C30, BPI-SF worst pain item, EQ-5D-5L	8.1.2				Table 2–4 [h]	x	Table 4
EORTC QLQ-BR23 (female participants only)	8.1.2				Table 2–4 [h]	x	
PRO-CTCAE	8.2.7				Table 2–4 [h]	x	
FACT-G single-item GP5	8.2.7				Table 2–4 [h]	x	Table 4
WPAI:GH	8.1.2				Table 2–4 [h]	x	
Plasma and *s*erum PK samples	8.4			Table 5	Table 5		x
Plasma and *s*erum ADA samples	8.8			Table 5	Table 5	*x*	x

Table 1 Schedule of Activities (cont.)

		Screening [a]		Induction Therapy Cycles [b] (21-day cycle)	Maintenance Therapy Cycles [c] (21-day cycle)	Treatment Discontinuation	Long-Term Follow-Up (Q3M) [d]
Day (Window)	Protocol Reference	–28 to enrollment	–7 to enrollment	1 (± 3 days)	1 (± 3 days)	28 days after final dose of Phesgo (± 3 days)	(± 15 days)
Blood and Plasma samples for biomarkers	8.7			Table 5	Table 5	x	
Blood sample for WGS/WES [n]	8.10.1				Table 5		
Blood sample for RBR [o]	8.10.2				Table 5		
Newly collected tumor tissue sample for biomarkers	8.7	Table 5 (Only if no archival tissue is available to assess eligibility)				Table 5 (Only if clinically indicated)	
Concomitant medications	6.8	x	x	x	x [h]		
Adverse events [p]	8.3, Appendix 2	x	x	x	x [h]	x	x
Survival and anti-cancer therapy follow-up	7					x	x

ADA = anti-drug antibody; CT = computed tomography (scan); eCRF = electronic Case Report Form; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ER=estrogen receptor; FSH = follicle-stimulating hormone; LHRHa = luteinizing hormone–releasing hormone agonist; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition (scan); NA = not applicable; PgR=progesterone receptor; PH= pertuzumab and trastuzumab; PK = pharmacokinetic; Q#W=every # weeks; Q#M= every # months; QD = daily; RBR = Research Biosample Repository; WES = whole exome sequencing; WGS = whole genome sequencing.

Table 1 Schedule of Activities (cont.)

Notes: Refer to the cited protocol reference for activity specific details.
Day 1 of the 1st cycle of induction therapy is the first dose of Phesgo. Participants should receive their first dose of Phesgo on the day of enrollment, if possible; if this is not possible, the first dose should occur no later than 2 days after enrollment. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Unscheduled visits may be performed if clinically indicated. Additional assessments may be performed as clinically indicated, per investigator discretion.

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and which fall into the specified screening window may be used; such tests do not need to be repeated for screening. See Section 5.4 for rescreening criteria.

[b] During the induction therapy phase, all participants will receive Phesgo in combination with a taxane (i.e., docetaxel or paclitaxel) for four to six cycles, as per the standard of care. At the investigator's discretion, participants who tolerate six cycles of induction therapy may be given up to two additional cycles of the same taxane+Phesgo, for a total of up to eight cycles (see Section 4.1.1.1). Participants who have received one or two cycles of Phesgo (or trastuzumab SC with pertuzumab IV, or PH IV) with docetaxel or paclitaxel prior to enrollment are eligible (see Section 5.1) and these additional cycles will count towards eligibility for the maintenance phase.

[c] Following the induction therapy phase, eligible participants will be randomized to one of two treatment arms (see Section 4.1.3). A 7-day window is permitted from randomization to Day 1 of the 1st cycle of study treatment in the maintenance phase.

[d] Follow-up visits are based on the date of the last dose of Phesgo and not on treatment discontinuation visit, (i.e., 3-month follow-up visit is 3 months after the date of final dose of Phesgo) with 1 month equal to 30 days. Follow-up visits are to be performed within $\pm$15 days. Participants who discontinue therapy in the induction therapy phase will enter into follow-up and only be followed for LVEF assessments, pregnancy testing, and long-term adverse events.

[e] Informed consent must be documented (paper or electronic, as applicable) before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of induction therapy treatment.

[f] Tumor assessments should be scheduled relative to the date of administration of the first induction therapy (on or off study, whichever is earlier), not the date of the previous tumor assessment. Participants who discontinue study treatment for any reason other than disease progression or death should continue to undergo tumor assessments as per the schedule, even if they start new anti-cancer therapy. Tumor assessment at the treatment discontinuation visit is not required for these participants.

[g] For participants at participating sites who have provided written informed consent to participate in mobile nursing visits, this assessment or procedure may be performed by a trained nursing professional at the participant's home or another suitable location.

[h] For participants at participating sites who have provided written informed consent to participate in mobile nursing visits, this assessment or procedure may be performed by a trained nursing professional at the participant's home or another suitable location (if allowed by country regulations), only for those visits where the participant is not required to attend the clinic for biomarker or PK sampling or ECG. On visits that require biomarker or PK sampling, or ECG to be performed, all assessments should be performed at the clinic.

Table 1 Schedule of Activities (cont.)

[i] ECHO or MUGA should be obtained during the last week (Days 15–21) of the 3rd induction therapy cycle (i.e., during the week prior to the 4th cycle *[including any off study induction cycles]*, to allow evaluation of the results before the next treatment cycle), and every 4th cycle thereafter. More frequent ECHO or MUGA assessments can be performed as clinically indicated. If not performed within the previous 6 weeks, ECHO or MUGA should be obtained at the treatment discontinuation visit. During the follow-up period, ECHO or MUGA should be obtained at 6 months and 12 months, and then annually thereafter (±28 days). Participants who discontinue study treatment for heart failure or LVEF decline should continue to undergo LVEF assessments according to this schedule, irrespective of the initiation of alternative systemic anti-cancer therapy,until event resolution, improvement to baseline status, no further improvement can be expected, or death.

[j] During the induction therapy phase, local laboratory assessment will be performed at each cycle and can be performed up to 3 days prior to Day 1 of each cycle. If screening laboratory assessments were performed within 3 days prior to Day 1 of the 1st induction therapy cycle, they do not have to be repeated. During the maintenance therapy phase, local laboratory assessment will be performed on Day 1 of the 1st and 2nd cycle and every 4 cycles thereafter (6th,10th,14th cycle etc.). Assessments can be performed up to 7 days prior to Day 1. Local assessments must be reviewed by the investigator for abnormalities prior to study treatment administration.

[k] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of induction therapy. Urine pregnancy tests will be performed at every cycle during induction therapy *(can be performed up to 3 days prior to Day 1)*, maintenance therapy *(can be performed up to 7 days prior to Day 1)*, at the treatment discontinuation visit, and monthly at Months 1 to 7 after the final dose of Phesgo. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Test results must be available prior to Phesgo injection. Note that participants are required to continue contraception for 7 months after final dose of Phesgo.

[l] Phesgo may be administered at the participant's home or another suitable location in the countries where this is possible per country regulations. If Phesgo is administered outside of the clinic then the Day 1 giredestrant dose for that cycle may also be administered outside of the clinic.

[m] Pre- and perimenopausal women and all men in Arm A who are receiving optional ET with an AI and pre- and perimenopausal women, and all men in Arm B will receive an LHRHa per local prescribing information. Pre- and perimenopausal women and men receiving treatment with tamoxifen may receive LHRHa at the discretion of the investigator. LHRHa therapy may be initiated up to 28 days prior to Day 1 of the 1st cycle of giredestrant, and should be initiated at least 28 days prior to the first AI administration.

[n] Not applicable for a site that has not been granted approval for WGS/WES. These WGS/WES samples are not applicable for China.

[o] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for participants at participating sites who have provided written informed consent to participate.

[p] After informed consent has been obtained but prior to enrollment and initiation of induction therapy, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of induction therapy, all adverse events will be reported until the treatment discontinuation visit (28 days after the final dose of study treatment). After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study drug (see Appendix 2). Heart failure (irrespective of causal relationship and for up to 3 years after Phesgo discontinuation), should also continue to be reported.

Table 2 Schedule of PRO Assessments [a]: Maintenance Phase Year 1 (up to Cycle 18 of maintenance) and Year 2 (up to Cycle 36 of maintenance)

Instrument	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 9	Cycle 12	Cycle 15	Cycle 18	Cycle 24	Cycle 30	Cycle 36
EORTC QLQ-C30, BPI-SF worst pain item, EQ-5D-5	x		x			x	x	x	x	x	x	x	x
EORTC QLQ-BR23 [b]	x					*x*		*x*		x	*x*	*x*	x
PRO-CTCAE, FACT-G GP5	x	x	x	x	x	x	x	x	x	x	x	x	x
WPAI:GH	x					x		x		x	x	x	x

[a] *Questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments (when possible), and prior to the administration of study treatment. PRO questionnaires will be completed by the patients on paper prior to administration of study drug (there is no window for the post-treatment timepoint). Questionnaires will be completed as noted in the SOA above and below. Questionnaires will be collected during the treatment period, and at the treatment discontinuation visit. They will also complete questionnaires during the long term follow-up years 1-5 following treatment discontinuation. Patients whose native language is not available are exempt from all PRO assessments. The Day 1 questionnaires for any cycle are not to be completed again in the event that it is determined following completion of the PROs that the Day 1 of the given treatment cycle will be delayed. Additionally, the timing of any subsequent PRO assessments will be based on the actual Day 1 of the given cycle (e.g., if it is determined that the start of treatment at Cycle 2 will be delayed a week, the Day 1 of Cycle 3 assessment will occur when the next Day 1 administration of treatment is planned).* If a participant receives Phesgo at home, PRO questionnaires will be provided for completion by a mobile nurse at the participant's home on their scheduled visit date.

[b] EORTC QLQ-BR23 is to be given immediately after the EORTC QLQ-C30 at those visits when both questionnaires are administered.

Table 3 Schedule of PRO Assessments [a]: Maintenance Phase Years 3 to 5 (Cycle 39 to Cycle 90 of maintenance)

	Year 3			Year 4			Year 5 [b]		
Instrument	Cycle *42*	Cycle 48	Cycle 54	Cycle *60*	Cycle 66	Cycle 72	Cycle *78*	Cycle 84	Cycle 90
EORTC QLQ-C30, BPI-SF worst pain item, EQ-5D-5L	x	x	*x*	x	x	*x*	x	x	*x*
EORTC QLQ-BR23 WPAI:GH	*x*	*x*	x	*x*	*x*	x	*x*	*x*	x
PRO-CTCAE, FACT-G GP5	x	x		x	x		x	x	

[a] If a participant receives Phesgo at home, PRO questionnaires will be provided for completion by a mobile nurse at the participant's home on their scheduled visit date.

[b] Participants who are treated for more than 5 years will continue assessments at the same pattern of frequency as Years 3–5.

Table 4 Schedule of PRO Assessments: Treatment Discontinuation and Follow-Up

		Follow-Up Year 1–2	Follow-Up Year 3–5
Instrument	Treatment Discontinuation	Q6M (±14 Days)	Q12M
EORTC QLQ-C30	x	x [a]	x [a]
EORTC QLQ-BR23	x [b]		
BPI-SF worst pain item	x	x [a]	x [a]
PRO-CTCAE	x		
FACT-G GP5	x	x [a]	x [a]
WPAI:GH	x		
EQ-5D-5L	x	x [a]	x [a]

[a] May be completed via phone interview.

[b] EORTC QLQ-BR23 is to be given immediately after the EORTC QLQ-C30 at those visits when both questionnaires are administered.

Table 5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Screening		
Visit	Timepoint	Sample Type
(Day –28 to Day –1)	NA	Archival tissue sample from the primary tumor (preferred) and/or metastatic sites must be submitted to assess HER2 status to confirm eligibility. Only participants who do not have tissue specimens that meet eligibility requirements may undergo a biopsy during the screening period. [a]
Induction Therapy Phase		
Visit	Timepoint	Sample Type
Day 1 of 1st Cycle on study	Prior to dosing	Biomarker (plasma)
		Pertuzumab/trastuzumab PK (serum)
		Pertuzumab ADA (serum)
		Trastuzumab ADA (serum)
		rHuPH20 ADA (plasma)

ADA = anti-drug antibody; FFPE=formalin-fixed, paraffin-embedded; HGRAC =Human Genetics Resources Administration of China; NA = not applicable; PgR=progesterone receptor;PK = pharmacokinetic.

Note: On treatment days, assessments should be performed prior to dosing, unless otherwise specified.

[a] A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections that meet the criteria outlined in Section 8.7 must be submitted prior to study enrollment. In exceptional circumstances, 11–19 slides are acceptable provided that other eligibility requirements are met (see Section 5); however, a minimum of 20 slides is highly preferred. For China, the number of slides required for eligibility will be based on HGRAC specifications.
If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment newly collected tumor biopsy is required. See Section 8.7 for specimen requirements. HER2 assessment for eligibility may be performed outside of the 28-day screening window. For participants who are randomized, ER and PgR status will be retrospectively assessed centrally. If possible, tissue from the same lesion should be used to assess ER and HER2 status.

Table 5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

Maintenance Phase (after Randomization)		
Visit	Timepoint	Sample Type
Day 1 of 1st Cycle	Prior to dosing [b]	Pertuzumab/trastuzumab PK (serum) [c]
		Giredestrant PK (plasma) [c]
		Pertuzumab ADA (serum) [c]
		Trastuzumab ADA (serum) [c]
		rHuPH20 ADA (plasma) [c]
		Biomarker (plasma)
		Biomarker (blood) [d]
		WGS/WES (blood)—participating sites only and not applicable for China [d]
		RBR (blood) —participants who have consented, participating sites only and not applicable for China [d]
	3 hours post giredestrant dose (±1 hour)	Giredestrant PK (plasma) [c]
Day 1 of 2nd Cycle	Prior to dosing [b]	Biomarker (plasma)
Day 1 of 4th Cycle	Prior to dosing [b]	Pertuzumab/trastuzumab PK (serum) [c]
		Giredestrant PK (plasma) [c]
		Pertuzumab ADA (serum) [c]
		Trastuzumab ADA (serum) [c]
		rHuPH20 ADA (plasma) [c]
	3 hours post giredestrant dose (± 1 hour)	Giredestrant PK (plasma) [c]
Day 1 of 6th Cycle	Prior to dosing [b]	Biomarker (plasma)
Day 1 of every 4th Cycle thereafter (i.e., 10th, 14th, 18th Cycle etc.) for the first 2 years and then every 6th Cycle up to 4 years of maintenance treatment	Prior to dosing [b]	Biomarker (plasma)

ADA = anti-drug antibody; NA = not applicable; PK = pharmacokinetic; RBR = Research Biosample Repository; WES = whole exome sequencing; WGS = whole genome sequencing.

Note: On treatment days, assessments should be performed prior to dosing, unless otherwise specified.

[b] The pretreatment samples can be collected up to 3 days prior to Cycle X Day 1.

[c] Only for participants *in* Arm B

[d] If missed at this timepoint, these blood samples can be collected at any point in the study.

Table 5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

Treatment Discontinuation, Disease Progression, and Long-Term Follow-Up		
Visit	Timepoint	Sample Type
	Treatment Discontinuation [e]	Biomarker (plasma) [f]
		Pertuzumab ADA (serum) [c]
		Trastuzumab ADA (serum) [c]
		rHuPH20 ADA (plasma) [c]
		Pertuzumab/trastuzumab PK (serum) [c]
	Disease Progression	Biomarker (plasma)
		Biomarkers (Tumor tissue sample)—if deemed clinically feasible [g]

ADA = anti-drug antibody; PK = pharmacokinetic.

[e] Participants who discontinue study treatment will return to the clinic for a treatment discontinuation visit 28 (± 3) days after their final dose of Phesgo.

[f] These biomarker plasma samples are required at treatment discontinuation for participants who discontinue for reasons other than progression of disease. If treatment is discontinued due to disease progression, the treatment discontinuation sample does not apply and only the disease progression sample needs to be collected. Following disease progression, the collection of plasma samples for biomarkers is no longer required. The plasma sample collection at disease progression (as defined for the primary efficacy endpoint) should occur within 40 days after disease progression or prior to start of the next systemic anti-cancer therapy, whichever is sooner.

[g] A representative FFPE tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), is not acceptable. The tissue sample collection should occur within 40 days after disease progression or prior to start of the next systemic anti-cancer therapy, whichever is sooner.

2. INTRODUCTION

2.1 STUDY 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).

2.2 BACKGROUND

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 (also known as HER2/neu or erbB2) (Burnstein et al. 2005). 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 (Slamon et al. 1987; Toikkanen et al. 1992; Andrulis et al. 1998).

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) (Baselga et al. 2012; Swain et al. 2015; Denduluri et al. 2018; Giodarno et al. 2018; Cardoso et al. 2020).

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 (Baselga et al. 2012; Gianni et al. 2012; Schneeweiss et al. 2013; Loi et al. 2016).

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 (Cortés et al. 2011). 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 (Rimawi et al. 2018).

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. Upon binding, giredestrant induces an inactive conformation to the ER LBD, as measured by displacement of co-activator peptides. 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.

Despite advances in early diagnosis and curative multimodality treatments, some patients may still experience a metastatic recurrence or present with “de novo” metastatic breast cancer (MBC). In this setting, the main goals of treatment are to improve the quality of life and prolong patient survival as there still is not a cure (Cardoso et al. 2020). Thus there continues to be a need for treatments with better benefit–risk profiles that prolongs PFS and other survival endpoints of patients with ER-positive, HER2-positive ABC.

Detailed information on Phesgo and giredestrant is provided in the respective Phesgo and Giredestrant Investigator's Brochures.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the efficacy and safety of giredestrant in combination with Phesgo in participants with previously untreated, locally-advanced unresectable, or metastatic, ER-positive HER2-positive BC, following four to six cycles of induction therapy with Phesgo+taxane (i.e., docetaxel or paclitaxel, as per the standard of care).

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 (Jhaveri et al. 2021).

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 (Hurvitz et al. 2021). 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 PH (Witters et al. 1997; Kunisue et al. 2000; Kaufman et al. 2009; Leary et al. 2010;

Shwarzberg et al. 2010; Wang et al. 2011; Huober et al. 2012; Rimawi et al. 2018). These patients are more frequently identified as having luminal BC subtypes compared to ER-negative, HER2-positive disease, which relies more intensely on the ER pathway, and frequently experience an intrinsic molecular subtype shifting/increased predominance from HER2-enriched to luminal BC upon chemotherapy + anti-HER2 therapy exposure (Perou et al. 2000; Carey et al. 2016; Cejalvo et al. 2017; Brasó-Maristany et al. 2020). 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 (Lambertini et al. 2019). 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 (Robertson et al. 2012; Ellis et al. 2015; Robertson et al. 2016).

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 (Kaufman et al. 2009; Huober et al. 2012; Rimawi et al. 2018; Jhaveri et al. 2021; Hurvitz et al. 2021).

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.

Refer to Appendix 3 for information on anticipated risks and risk mitigation measures for Phesgo and giredestrant, including guidelines for managing adverse events associated with Phesgo or giredestrant.

More detailed information about the known and expected benefits and risks, and reasonably expected adverse events of Phesgo and giredestrant may be found in the respective Investigator's Brochures.

Taking into account giredestrant's 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.

2.3.1 COVID-19 Benefit–Risk Assessment

Based on the mechanisms of action and the observed clinical safety profiles, it is not anticipated that treatment with Phesgo plus giredestrant will compromise the immune system nor increase the likelihood or the severity of infection with SARS-CoV-2. There is an increased risk of exposure to SARS-CoV-2 associated with hospital visits. This risk can be minimized by complying with local guidelines and hospital policies. Metastatic cancer is a life-threatening disease, and treatment with giredestrant and Phesgo is expected to provide a clinically meaningful improvement in PFS; therefore, the anticipated benefit–risk of this study remains positive in the setting of the *coronavirus disease 2019 (*COVID-19*)* pandemic.

Given that the study drugs, Phesgo and giredestrant, are not expected to increase the risk or severity of COVID-19, no specific SARS-CoV-2 safety management guidelines are deemed necessary, and patients should be treated as per institutional standards of care with decisions for interruptions of study drugs taken by the sites based on the severity of the infection. Refer also to the guidelines provided for Phesgo and giredestrant in Appendix 3, respectively, and the local labels for other therapies. Participants with serious infection within 14 days prior to enrollment are excluded; however, no testing for SARS-CoV-2 is required. Investigational sites will be specifically trained in the reporting of any occurrences of COVID-19, and the safety of participants will continue to be monitored regularly by both the Sponsor and IDMC.

3. OBJECTIVES AND ENDPOINTS

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). Specific objectives and corresponding endpoints for the study are outlined in Table 6.

The primary comparison of interest is the hazard ratio (HR) of PFS. The primary trial objective is to demonstrate superiority of the Phesgo plus giredestrant arm over the Phesgo arm.

In this protocol, “induction therapy” refers to treatment with Phesgo + taxane and "study maintenance treatment" refers to Phesgo plus giredestrant or Phesgo.

The primary and secondary estimands, as introduced in ICH-E9 addendum (ICH 2020), are defined in Section 9.4.

Table 6 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.

Table 6 Objectives and Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• To evaluate the efficacy of Phesgo plus giredestrant compared with Phesgo	• Mean and mean changes from baseline score in disease/treatment-related symptoms by cycle and between treatment arms as assessed by all symptom items/scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 • Proportion of participants reporting a clinically meaningful deterioration in pain severity, defined as a ≥2-point increase from baseline on the "worst pain" item score from the BPI-SF questionnaire
• To evaluate effects of Phesgo plus giredestrant compared with Phesgo on work productivity and activity	• Changes in patient-reported WPAI scores at specified timepoints
• To evaluate health utility of participants treated with Phesgo plus giredestrant compared with Phesgo to generate utility scores for use in economic models	• Utility scores of the EQ-5D-5L questionnaire
• To evaluate the *tolerability* of Phesgo plus giredestrant compared with Phesgo from the participant's perspective	• Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities (nausea, vomiting, diarrhea, rash, joint pain, fatigue, hot flashes), as assessed through use of the NCI PRO-CTCAE • Proportion of participants reporting each response option at each assessment timepoint by treatment arm for treatment side-effect bother single-item GP5 from the FACT–G • Change from baseline in symptomatic treatment toxicities and treatment side-effect bother, as assessed through use of the PRO-CTCAE and the overall treatment side-effect bother item, respectively
• To characterize the giredestrant, pertuzumab, and trastuzumab PK profile when given in combination	• *Concentrations* of pertuzumab and trastuzumab in serum at specified time points • *Plasma concentrations of giredestrant* at specified time points

BPI-SF= Brief Pain Inventory-Short Form; CTCAE = Common Terminology Criteria for Adverse Events; *FACT–G =Functional Assessment of Cancer Therapy–General*; PK = pharmacokinetic; PRO-CTCAE = *Patient-R*eported Outcomes Common Terminology Criteria for Adverse Events; WPAI:GH= Work Productivity and Activity Impairment Questionnaire: General Health.

Table 6 Objectives and Endpoints (cont.)

Exploratory Objectives (cont.)	Corresponding Endpoints
• To evaluate the potential relationships between Phesgo and giredestrant exposure and the safety, efficacy, immunogenicity, or biomarker endpoints *when Phesgo and giredestrant are given in combination*	• Relationship between pertuzumab PK and efficacy, safety, immunogenicity, or biomarker endpoints • Relationship between trastuzumab PK and efficacy, safety, immunogenicity, or biomarker endpoints • Relationship between giredestrant PK and efficacy, safety, immunogenicity, or biomarker endpoints
• To evaluate the immune response to pertuzumab, trastuzumab, and rHuPH20	• Incidence of pertuzumab ADAs during the study relative to the prevalence of ADAs at baseline • Incidence of trastuzumab ADAs during the study relative to the prevalence of ADAs at baseline • Incidence of rHuPH20 ADAs during the study relative to the prevalence of ADAs at baseline
• To evaluate potential effects of ADAs *when Phesgo and giresdestrant are given in combination*	• Relationship between pertuzumab ADA status and efficacy, safety, or PK endpoints • Relationship between trastuzumab ADA status and efficacy, safety, or PK endpoints • Relationship between rHuPH20 ADA status and efficacy, safety, or PK endpoints
• To identify and/or evaluate biomarkers that are predictive of response to Phesgo and giredestrant (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to Phesgo and giredestrant, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of Phesgo and giredestrant activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood, plasma and tumor tissue (listed in Section 8.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; PK = pharmacokinetic.

4. STUDY DESIGN

4.1 OVERALL DESIGN

4.1.1 Overview of Study 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. 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. See Section 4.1.1.1). 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 (see Section 5.1) 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 (see Section 4.1.3) 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.

Screening and enrollment into the induction therapy phase will be carefully monitored by the Sponsor to achieve a total randomization of approximately 730 participants in the maintenance therapy phase. Participants who are still in the induction therapy phase after this target is reached will be allowed to enter the maintenance therapy phase, if they are deemed eligible by the investigator.

Participants will be followed for safety for 28 days after the final dose of study treatment, including a treatment discontinuation visit at 28 days (±3 days) after the final dose of Phesgo. Thereafter, information on survival and new anti-cancer therapy will be collected every 3 months until death (unless the participant withdraws consent or the Sponsor terminates the study). The survival follow-up period for participants remaining in the study will conclude at the time of the final overall survival (OS) analysis.

Participants will undergo tumor assessments at screening, at Week 9 (to ensure at least one evaluation is conducted during the induction therapy phase), then every 12 weeks up to 36 months then every 18 weeks thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 (see Section 8.1.1).

Efficacy analyses will be based on the local radiologist's or investigator's tumor assessments. All radiographic images, photographs, and clinical information will be collected by the Sponsor to enable a blinded independent central review (BICR) audit of a prespecified subset of PFS data by an Independent Review Committee (IRC). IRC membership and procedures will be detailed in an IRC charter whereas audit strategy and methodology will be detailed in a separate BICR audit plan.

An independent Data Monitoring Committee (iDMC) will evaluate unblinded safety data on a regular basis during the study, including a review of safety data after 25 participants in Arm B complete two cycles of maintenance treatment, in order to ensure the combinability of Phesgo and giredestrant. The iDMC will follow a charter that outlines the iDMC's roles and responsibilities and the timing of iDMC meetings. The iDMC will thoroughly review the available cumulative safety data and can make recommendations to modify study conduct, suspend enrollment, change the eligibility criteria or safety evaluations, or terminate the study if there is evidence of undue risk to the study participants. All summaries and analyses for the iDMC's review will be prepared by an external independent Data Coordinating Center (iDCC). Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

*Patient-r*eported outcome (PRO) instruments will be completed by participants to evaluate the treatment impact from the participant's perspective.

All participants will be closely monitored for adverse events throughout the study, and adverse events will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

A study schema is provided in Section 1.2 (see Figure 1). Refer to Section 1.3 for a schedule of activities (Table 1), schedule of PRO assessments (Table 2, Table 3, and Table 4) and a sample collection schedule (Table 5).

4.1.1.1 Patient Input into Study Design

Five representatives from different organizations within the HER2-positive/ER-positive MBC patient community were interviewed and asked to provide feedback on the following aspects of the trial:

- Study design, endpoints, inclusion and exclusion criteria for maintenance treatment, schedule of assessments and PROs
- Recruitment and retention (e.g., inclusivity of underserved patient communities, potential recruitment challenges, possible retention challenges)

This feedback was considered while developing the protocol.

4.1.2 Induction Therapy Phase

During the induction therapy phase, all participants will receive Phesgo in combination with a taxane (i.e., docetaxel or paclitaxel) for four to six cycles, as per the standard of care. Refer to Section 6.1 for study drug information.

At the investigator's discretion, participants who tolerate six cycles of induction therapy well and in the absence of PD or limiting toxicity, may be given up to two additional cycles of the same combination taxane+Phesgo, for a total of up to eight cycles.

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 (see Section 5.1), provided they have not experienced PD or limiting toxicity. Any off-study cycles will count towards the four to eight cycles allowed and eligibility for the maintenance phase.

Participants who are unable to tolerate the assigned taxane and discontinue prior to the minimum of four cycles will discontinue all study treatment and enter the follow-up phase. The participant will be treated as per the standard of care at the discretion of the investigator, as clinically indicated. See the schedule of activities (Section 1.3) for assessments to be completed for participants who discontinue during the induction therapy phase.

4.1.3 Maintenance Phase

Following the induction therapy phase, participants who meet the following criteria will be eligible for the maintenance phase:

- Complete a minimum of four cycles of induction therapy, defined as either:
  - 4 Phesgo injections+4 docetaxel infusions

    or
  - 4 Phesgo injections+12 paclitaxel infusions

  Note: If a participant has received one or two cycles of induction therapy prior to enrollment, these cycles are to be counted towards the required number of cycles for eligibility of the maintenance phase (e.g., if the participant was given one cycle of Phesgo [or trastuzumab SC with pertuzumab IV, or PH IV] +docetaxel prior to enrollment, a minimum of 3 on-study cycles of Phesgo+docetaxel are required prior to entering the maintenance phase)
- Achieve a minimum of stable disease (SD) (i.e., did not experience progressive disease [PD]) according to RECIST v1.1 at the last tumor assessment during the induction therapy phase
- Left ventricular ejection fraction (LVEF) of $\geq$50% at the last assessment during the induction therapy phase

Eligible participants will be randomized in a 1:1 ratio to one of two treatment arms: Crossover between the two treatment arms will not be allowed. Prior to *enrolling* a participant, investigators must decide and document if optional ET will be prescribed according to the standard of care, in the event that the participant is randomized to Arm A.

- 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 (ETs can include an AI or tamoxifen). Pre- and perimenopausal women or men who receive an AI must also receive a luteinizing hormone–releasing hormone agonist (LHRHa). Alternatively, women who are pre- or perimenopausal can be treated with bilateral oophorectomy. Per Investigator discretion, women who are pre- or perimenopausal or men who receive tamoxifen may also receive LHRHa (see Section 6.1.4).
- Arm B (Phesgo plus giredestrant: experimental arm): Participants will receive giredestrant 30 mg orally (PO) once daily (QD) on Days 1−21 of each 21-day cycle in combination with Phesgo subcutaneously Q3W. Pre- and perimenopausal women, and all men will receive a LHRHa every 28 days and up to 28 days prior to the first giredestrant dose. Alternatively, pre- or perimenopausal women can be treated with bilateral oophorectomy (see Section 6.1.4).

See Section 6.1 for description of study treatments.

The following stratification factors will be applied*:*

- Disease status: visceral metastasis *(brain/lung/liver)* versus non-visceral metastasis
- Type of stage IV presentation: de novo metastatic versus recurrent metastatic disease

  Note: De novo MBC is defined as BC that presents as Stage IV disease at first diagnosis.
- Intention to give ET of investigator's choice: yes versus no
- Overall response (OR) during the induction therapy phase: PR/CR versus SD (or Non-CR/Non-PD for participants with non-measureable disease).

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

This study will enroll men and women with ER-positive, HER2-positive ABC, who are considered appropriate for treatment with induction therapy in routine clinical practice.

The Phase III trial, CLEOPATRA (Study WO20698), demonstrated that first-line treatment with docetaxel + PH improves PFS and OS compared to docetaxel + placebo and trastuzumab, for patients with HER2-positive ABC (Baselga et al. 2012; Swain et al. 2015). Due to the demonstrated survival advantages and manageable toxicity profile, treatment with docetaxel in combination with PH has become the gold standard in this

setting (Giordanno et al. 2018; Cardoso et al. 2020). However, there continues to be a high unmet medical need in this patient population given that 50% of patients who are treated with first-line therapy experience disease progression within 18.5 months, and 42.4% will die within 4 years.

Approximately 50%–60% of patients with HER2-positive BC also have concurrent hormone receptor expression (Montemurro et al. 2013). A bi-directional cross-talk between the HER-family and ER has been fully characterized at the cellular level, whereby suppression of either receptor alone is associated with upregulation of the other, ultimately leading to resistance to therapy (Cortés et al. 2011). The Phase II trial, PERTAIN (Study MO27775), demonstrated the beneficial effect of treatment with dual HER2–blockade (i.e., PH) with an AI compared with single HER2–blockade (i.e., trastuzumab) with an AI (Rimawi et al. 2018). It remains unknown, however, if the addition ET to maintenance PH following chemotherapy discontinuation outperforms maintenance PH alone.

4.2.2 Rationale for Control Group

The control arm (i.e., maintenance Phesgo) will be used to ascertain the individual contribution of giredestrant to the efficacy of Phesgo in the maintenance phase of this study (WO43571).

Participants in this arm will be receiving the current standard-of-care treatment (i.e., PH with docetaxel or paclitaxel induction therapy followed by maintenance PH) for patients with previously untreated ER-positive, HER2-positive ABC (Miles et al. 2020).

4.2.3 Rationale for Choice of Phesgo

Phesgo is a ready-to-use formulation of PH co-formulated in a single vial for SC injection use with recombinant human PH20 hyaluronidase (rHuPH20). Phesgo administration has been proven equivalent to IV PH from a PK, efficacy, and safety perspective (Tan et al. 2020). Phesgo can be administered in 5–8 minutes versus hours and is preferred by most patients compared to IV administration of PH (O'Shaughnessy et al. 2020). Phesgo is the standard of care and has received health authority approval in the same settings as the IV formulations: Phesgo is approved in the United States, and can be administered at home by a health-care professional (FDA Press release 2020). Phesgo is also approved in the European Union, and several other countries in the world. The indications cover the use in patients with HER2-positive EBC and MBC.

The choice of the SC formulation of PH versus IV is expected to enhance the flexibility of care and improve patient experience when used with an oral ET. Therefore, Phesgo will be used in this study for PH administration.

4.2.4 Rationale for Taxane Choice and Number of Cycles

Taxanes are anti-neoplastic agents that bind to free tubulin within the cell and promote the assembly of tubulin into stable microtubules while simultaneously inhibiting their

disassembly (Bissery 1995). This mode of action leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, blocking cells in the M-phase of the cell cycle and leading to cell death. Extensive phase II and III data have led to regulatory approvals for its use either in combination or as monotherapy for the treatment of BC.

Docetaxel is a semi-synthetic analog of paclitaxel, which was the first taxane to be identified. Both trastuzumab and pertuzumab have been successfully administered with docetaxel and paclitaxel. Importantly, both taxanes have been shown equivalent upon combination with PH for treating patients with HER2-positive MBC (Miles et al. 2020).

PH with at least six cycles of docetaxel or paclitaxel induction therapy followed by maintenance PH is the standard of care for patients with previously untreated ER-positive, HER2-positive ABC (Giordanno et al. 2018; Cardoso et al. 2020).

In CLEOPATRA, it was recommended that patients receive at least six cycles of docetaxel with PH. Patients who received six cycles derived similar survival benefits with the addition of pertuzumab to trastuzumab, 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). Additionally, in PERUSE (Study MO28047), the median number of cycles for both taxanes (i.e., docetaxel and paclitaxel) was six.

Based on this, during the induction therapy phase, participants will be treated with investigator's choice of taxane, consisting of docetaxel or paclitaxel, for a minimum of four cycles (if limiting toxicities occur) and up to six cycles, before being randomized. Nonetheless, 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.

4.2.5 Rationale for Investigator's Choice of Endocrine Therapy

In CLEOPATRA, ET during maintenance PH was not allowed for patients with ER-positive, HER2-positive ABC, due to the absence of safety data for this combination at the time of the trial. This is reflected in the Perjeta and Phesgo labels, where there is no mention of using ET after chemotherapy discontinuation. Therefore, Phesgo alone is an optimal treatment regimen for the control arm.

Nonetheless, given the bi-directional cross-talk between ER and HER2 (Cortés et al. 2011), and the emergence of exploratory data pointing towards improved survival outcomes with the addition of maintenance ET to PH (Loft et al. 2020) it is reasonable to add maintenance ET to PH according to international guidelines (Giordano et al. 2018;

Cardoso et al. 2020). In clinical practice there is an increase in the use of ET in this setting. For instance, in PERUSE (Study MO28047) and MetaPHER (Study BO29159), maintenance ET with PH was allowed per investigator's discretion and, consequently, 30% to 44% of patients with hormone receptor-positive, HER2-positive ABC received ET (Miles et al. 2020; Kuemmel et al. 2021). Therefore, allowing investigator's choice of ET, or no ET is expected to give flexibility to investigators in the control arm, as well as to reflect real world clinical practice.

4.2.6 Rationale for Primary Endpoint

PFS is regarded as a clinically relevant measure of treatment benefit and for many years has been shown to be an approvable endpoint in the setting of HER2-positive ABC for several drugs, including pertuzumab in addition to trastuzumab plus docetaxel. In the primary analysis of the CLEOPATRA study, with only a median follow-up time of up to 18.7 months, median PFS for pertuzumab added to trastuzumab plus docetaxel was improved over placebo added to trastuzumab plus docetaxel (18.5 months vs.12.4 months). The associated PFS HR was 0.62 (95% CI [0.51, 0.75], $p < 0.0001$) (Baselga et al. 2012).

This Phase III study aims to improve median PFS during the maintenance phase of treatment by 6.7 months with the combination of giredestrant with the standard of care set by CLEOPATRA (maintenance PH). Further details on the statistical assumptions are provided in Section 9.4.

CLEOPATRA warranted a long median follow-up time, of 50 months, to demonstrate a statistically significant superiority of OS with pertuzumab over placebo (56.5 months vs. 40.8 months, respectively [HR of 0.68; 95% CI, 0.56 to 0.84; $p < 0.001$) (Swain et al. 2015). In this sense, PFS is expected to provide a shorter read out for this study and potentially enable earlier access to a new beneficial therapy with giredestrant, should the trial be positive.

The PFS during the maintenance treatment phase (after randomization) will be determined by the investigator according to RECIST v1.1.

4.2.7 Rationale for Stratification Factors

To balance the clinical risk factors between the two study arms, randomization will be stratified using a permuted-block randomization scheme. The stratification factors are as follows:

- Disease status: visceral metastasis *(brain/lung/liver)* versus non-visceral metastasis
- Type of stage IV presentation: de novo metastatic versus recurrent metastatic disease

  Note: De novo MBC is defined as BC that presents as Stage IV disease at first diagnosis.

- Intention to give ET of investigator's choice: yes versus no
- OR during the induction therapy phase: PR/CR versus SD (or Non-CR/Non-PD for participants with non-measureable disease)

The presence of visceral disease has been long recognized as a negative prognostic factor in patients diagnosed with MBC, including in HER2-positive disease (Cutler et al. 1969; Solomayer et al. 2000; Largillier et al. 2008). In the primary analysis of CLEOPATRA, a significant treatment effect with the addition of pertuzumab to trastuzumab plus docetaxel compared with the addition of placebo, by covariate interaction, was observed for disease status ($p = 0.0332$). In subgroup analyses, a stronger treatment effect was observed in the subgroup of patients with visceral disease (HR = 0.55, [0.45, 0.68]) than in those with non-visceral disease (HR = 0.96, [0.61, 1.52]), however, the latter subgroup was small (only 22% of the trial population). The median PFS was estimated to be 10.4 months in the placebo arm compared to 17.2 months in the pertuzumab arm in the subgroup with visceral disease, whereas the median PFS was 17.3 months vs. 20.8 months, respectively, in the subgroup with non-visceral disease. The prognostic effect of disease status, whereby patients with HER2-positive ABC and visceral disease have worse clinical outcomes compared to patients with non-visceral disease has also been observed in other randomized trials with pertuzumab (PERTAIN [Study MO27775], PHEREXA [Study MO22324], and PUFFIN [Study YO29296]). Therefore, given the strong prognostic effect of disease status on PFS in the setting of HER2-positive ABC, it is important to stratify randomization accordingly (visceral metastasis *[brain/lung/liver]* vs. non-visceral metastasis).

Patients with HER2-positive BC that initially presents with metastatic disease (de novo metastatic) have better clinical outcomes with first-line anti-HER2 therapies compared to those that experience a metastatic recurrence and have been previously exposed to anti-HER2 therapies in the early setting (Yardley et al. 2014; Tripathy et al. 2020). This observation possibly stems mainly from acquired resistance mechanisms to anti-HER2 therapies in place by the time these patients are re-exposed to treatment (Tripathy et al. 2020). Therefore, given the prognostic effect of Type of stage IV presentation on PFS and other clinically relevant outcomes in the setting of HER2-positive ABC, it is important to stratify randomization accordingly (de novo metastatic vs. recurrent metastatic disease).

As outlined in the background section, the use of ET in the maintenance setting is optional in clinical practice. A few clinical characteristics may help physicians determine whether or not to offer ET with Phesgo following chemotherapy induction, that may predict for a higher endocrine sensitivity. None of these clinical characteristics were prospectively validated in this setting, although they have been shown to retain some predictive value for ET sensitivity in other disease settings, namely HER2-negative, hormone receptor-positive ABC.

Examples of such clinical characteristics may include a high degree of IHC ER expression, concomitant PgR expression, predominant bone disease, amongst others. In this sense, controlling indirectly for these clinical characteristics by means of stratifying according to the investigator decision of giving ET (yes vs. no) will ensure a better balance of baseline prognostic factors between treatment arms.

Obtaining an OR, a composite of RECIST-assessed partial response (PR) plus complete response (CR), with treatment with chemotherapy has long been correlated with PFS and OS in ABC (Bruzzi et al. 2005; Burzykowski et al. 2008). Similarly, OR to chemotherapy plus anti-HER2 therapies is also strongly correlated with improved PFS in first-line HER2-positive ABC. In a Phase III randomized clinical trial testing the non-inferiority of a biosimilar trastuzumab plus taxane versus Herceptin plus taxane, OR at Week 24 predicted PFS at Week 48 (Rugo et al. 2021). Importantly, at Week 48, patients were under maintenance therapy with trastuzumab, analog*ous* to the maintenance phase of this study. Therefore, given the strong prognostic effect expected for OR with taxane+Phesgo on PFS in the setting of HER2-positive ABC, it is important to stratify randomization accordingly (PR/CR vs. SD). Participants without measurable disease cannot be classified as achieving a PR per RECIST v1.1, only CR or non-CR/non-PD. Therefore, only for stratification purposes, participants without measurable disease shall be considered as: CR/PR for those achieving a CR, and SD for those achieving a non-CR/non-PD. Those achieving PD during the induction therapy phase cannot be randomized.

4.2.8 Rationale for Biomarker Assessments

Primary and/or metastatic archival tumor specimens will be collected and tested for expression of HER2 by a central laboratory during the screening period to determine eligibility. ER status for eligibility will be assessed locally. Patients with ER-positive, HER2-positive tumors have a significantly worse prognosis compared to patients with other ER-positive tumors, and account for around 50% of the HER2-positive tumors (Ding et al. 2019). In addition, ER status in HER2-positive disease is associated with different responses depending on the setting and treatment (neoadjuvant and adjuvant), location and type of metastases (Vaz-Luis et al. 2013; Arciero et al. 2019). The cross–talk between the ER and HER2 pathways is complex and involves different downstream targets, including PI3K and MAPK (Shou et al. 2004; Wu et al. 2015; Lousberg et al. 2016). Understanding the driver can help in better identify patients who will respond to different treatments. Several studies show that ER signaling acts as a survival mechanism for HER2-positive disease (Wang et al. 2011; Giuliano et al. 2015).

In addition to the assessment of HER2, ER, and PgR status will be retrospectively centrally assessed for all enrolled patients. Other biomarkers for exploratory research, such as potential predictive and prognostic biomarkers related to the clinical benefit of Phesgo and giredestrant, mechanisms of resistance, or tumor type, may be analyzed, as

well as biomarkers related to the HER2 and ER/PgR pathways and the classification of the PAM50 subtypes.

If available, primary and metastatic tumors will be collected in order to assess whether changes in biomarker profiles are related to potential resistance mechanisms or related to efficacy endpoints (exploratory biomarker objective). Tumor tissue will also be collected by biopsy at the time of first evidence of disease progression, if deemed clinically feasible by the investigator, to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of Phesgo and giredestrant.

Plasma samples will be collected prior to the start of the induction therapy and prior to the maintenance phase (together with blood sample), during the maintenance phase, and at disease progression to evaluate changes in surrogate biomarkers. Changes in biomarkers such as circulating tumor DNA (ctDNA) may provide evidence of biologic activity of study treatment or may be relevant for monitoring disease response or progression. Correlations between biomarker levels and efficacy endpoints will be explored to identify blood-based biomarkers that might be predictive of which patients are more likely to have a better prognosis, to benefit from study treatment, or to experience disease progression. Correlations between biomarker levels and safety endpoints may also be explored.

Tissue samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or whole exome sequencing (WES) to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. DNA extracted from blood will be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events, or can lead to improved adverse event monitoring or investigation.

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

4.2.9 *Rationale for Pharmacokinetic Sample Collection Schedule*

Pharmacokinetic samples will be collected in this study to characterize the pharmacokinetics of giredestrant, and trastuzumab and pertuzumab (within Phesgo).

The pharmacokinetics of giredestrant (as monotherapy), pertuzumab and trastuzumab (within Phesgo) have been well characterized in previous studies. Sparse PK samples of giredestrant, trastuzumab and pertuzumab will be collected as outlined in Table 5 and enable the potential population PK and exposure-response analysis for giredestrant, pertuzumab and trastuzumab when Phesgo and giredestrant are given in combination.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

4.3.1 Phesgo

The Phesgo dose and schedule selected to be used in this study are consistent with the prescribing information. An initial loading dose (1200 mg pertuzumab, 600 mg trastuzumab, 30,000 U rHuPH20) followed by a maintenance dose (600 mg pertuzumab, 600 mg trastuzumab, 20,000 U rHuPH20) Q3W will be administered subcutaneously.

The loading dose and maintenance dose of pertuzumab SC within Phesgo were determined in Part 1 of the Phase I BO30185 study and confirmed in Part 2 of the study. The dose of trastuzumab within Phesgo was previously established in a Phase Ib dose–finding study (BO22023) and confirmed in the Phase III study BO22227. rHuPH20, a human recombinant hyaluronidase within the fixed-dose combination, is given at a standard concentration of 2000 U/mL.

Study WO40324 investigated the efficacy and safety of pertuzumab/trastuzumab SC versus pertuzumab/trastuzumab IV in participants with EBC and confirmed that these doses were non-inferior in Cycle 7 by serum C_{trough} (Tan et al. 2019).

See the Phesgo Investigator's Brochure for additional information.

4.3.2 Giredestrant

This study will evaluate giredestrant at 30 mg taken orally (PO) QD administered on Days 1–21 of each 21-day cycle, beginning on Day 1 of Cycle 1 of the maintenance phase. This dose and regimen was selected as it is well tolerated and most likely to achieve clinical benefit based on available preclinical and clinical data, which are summarized below.

Giredestrant exhibited dose-dependent anti-tumor activity in xenograft models of ER-positive BC, including in a patient-derived xenograft model that harbors an activating

ESR1 mutation (ER.Y537S). Maximal activity of giredestrant occurred at human dose equivalents greater than 10 mg, and no further ER depletion nor inhibition of ER transcription activity was observed at doses corresponding to clinical doses higher than 30 mg.

In addition, preclinical data demonstrate the superiority of giredestrant to fulvestrant, at clinical doses of ≥30 mg (Metcalfe et al. 2018; Wang et al. 2020) as demonstrated by deeper ER pathway inhibitions and better physico-chemical properties, which results in a higher bioavailability of giredestrant.

Giredestrant has favorable PK properties with a mean half-life ranging from 25.8–43.0 hours in the dose range of 10–250 mg, supporting the once-daily dosing regimen.

In Study GO39932, giredestrant given at 30 mg orally QD was associated with more than 90% ER target engagement as measured by 18F-fluoroestradiol PET scan (FES-PET). All participants treated with giredestrant experienced ≥75% in the corrected standardized uptake value, a decrease that has been associated with clinical benefit (van Kruchten et al. 2015).

In Study GO39932, changes in pharmacodynamic and activity biomarkers (ER, PgR, and Ki67 protein expression by IHC) indicated that reductions in ER pathway signaling and cell proliferation by giredestrant were achieved with a 30-mg dose.

At 30 mg orally daily, the clinical benefit rate (CBR; ≥24 weeks on therapy) in participants evaluable for CBR was 55%, response rate (RR) was 14.6%, and median PFS was 7.2 months. The anti-tumor activity was consistent across all the dose levels (10–250 mg), except for the 10-mg dose level at which the CBR and median PFS were lower (for 10-mg dose, CBR was 16.7% and median PFS was 5.3 months) (clinical cutoff date [CCOD] 31 January 2021).

Overall, giredestrant was shown to be well tolerated at all dose levels with few Grade ≥3 (<5%) or serious adverse events (<2.5%) at any dose level that were considered related to giredestrant by the reporting investigators. There were no adverse events related to giredestrant that led to discontinuation of treatment from the single-agent arms and no clear trend for an increase in frequency or severity of adverse events, except for bradycardia/heart rate decrease that was dose related and largely asymptomatic. No adverse events of bradycardia were reported from study, from the 30-mg cohort as of the CCOD 31 January 2021.

Based on the preclinical and clinical data, and the comparable CBR seen at doses ≥30 mg, a daily dose of 30 mg was selected for this study.

See the Giredestrant Investigator's Brochure for additional information.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last scheduled procedure shown in the schedule of activities (see Section 1.3).

The end of this study is defined as the date of the at which the required number of deaths (387 OS events) for the final statistical analysis i.e., OS has been observed.

The end of the study is expected to occur approximately 86 months after the last participant is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

Treatment will continue until disease progression per RECIST v1.1, limiting toxicity, death, withdrawal of consent, or study termination by the Sponsor. The total duration of study participation for each individual is expected to range from 1 day to more than 86 months.

5. STUDY POPULATION

Approximately 812 participants with HER2-positive, ER-positive ABC (metastatic or locally-advanced not amenable to curative treatment) who have not previously received systemic non-hormonal anti-cancer therapy in the advanced setting will be enrolled into the induction therapy phase and ~730 will be randomized into the maintenance phase of this study. One or two cycles of prior Phesgo (or trastuzumab SC plus pertuzumab IV, or PH IV) with a taxane (docetaxel or paclitaxel) are allowed prior to enrollment.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

- Signed Informed Consent Form
- *Participants (females, regardless of menopausal status, and males) who are aged* ≥18 years at the time of signing Informed Consent Form
  - *For women: postmenopausal or premenopausal status, defined as follows:*

    A participant is considered postmenopausal if any of the following definitions are met:

    Prior bilateral oophorectomy

    Age ≥ 60 years

    Age <60 years and amenorrheic for 12 months or more in the absence of chemotherapy or ovarian suppression, and FSH and estradiol in the postmenopausal ranges

  - *Pre- or perimenopausal (i.e., not meeting the criteria for postmenopausal)*
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed and documented adenocarcinoma of the breast with metastatic or locally-advanced disease not amenable to curative resection.
  - HER2-positive ABC confirmed by a central laboratory prior to study enrollment. HER2-positive status will be determined based on primary or metastatic lesion and defined as 3+ by immunohistochemistry (IHC) and/or positive by HER2 amplification by in situ hybridization (ISH) with a ratio of ≥2 for the number of *HER2* gene copies to the number of signals for chromosome 17 copies. Participants will be eligible provided that at least one HER2 test (IHC or ISH) yields a positive result

    A representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections that meet the criteria outlined in Section 8.7 must be submitted prior to study enrollment. In exceptional circumstances, 11–19 slides are acceptable provided that other eligibility requirements are met; however, a minimum of 20 slides is highly preferred. For China, the number of slides required for eligibility will be based on Human Genetics Resources Administration of China (HGRAC) specifications.
  - Documented ER-positive tumor according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, assessed locally and defined as ≥1% of tumor cells staining positive for ER, preferentially based on the same lesion that was used to determine HER2 positivity.
- At least one measurable lesion and/or non-measurable disease evaluable according to RECIST version 1.1
  - Note for participants who receive induction therapy off study: baseline tumor assessments must meet the criteria as listed in Section 8.1.1.1.
- Disease-free interval from completion of adjuvant or neoadjuvant systemic non-hormonal treatment to recurrence of ≥6 months
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or1
- LVEF of at least 50% measured by ECHO or MUGA
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to enrollment:
  - ANC ≥1.5 x 10^9/L (1500 cells/μL) with one exception:

    Participants with benign ethnic neutropenia: ANC ≥1.3×10^9/L (1300/μL)
  - Platelet count ≥100,000 cells/μL
  - Hemoglobin ≥9.0 g/dL

    Participants may receive RBC transfusions to obtain this level

- Estimated creatinine clearance $\geq$30mL/min as calculated per institutional guidelines
- INR and aPTT $\leq$1.5 $\times$upper limit of normal (ULN) (except for participants receiving anticoagulation therapy)

  For participants receiving warfarin, a stable INR between 2 and 3 is required.

  For participants receiving heparin, PTT (or aPTT) between 1.5 and 2.5 ULN is required.

  If anticoagulation therapy is required for a prosthetic heart valve, stable INR between 2.5 and 3.5 is permitted.
- Serum AST and ALT $\leq 3 \times$ULN (for participants with documented liver metastasis: AST and ALT$\leq 5 \times$ULN)
- Serum total bilirubin (TBILI) $\leq$1.5$\times$ULN, except for participants with Gilbert syndrome ($\leq$ 3$\times$ULN), for whom direct bilirubin should be within the normal range
- Serum albumin $\geq$25 g/L (2.5 g/dL)

- For women of childbearing potential: Participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agree to refrain from donating eggs, as defined below:

  Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for 7 months after the final dose of Phesgo. A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of non-hormonal contraceptive methods with a failure rate of $<$1% per year include 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.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 7 months after the final dose of Phesgo to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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 preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

5.1.1 Maintenance Phase Criteria

Participants are eligible to be randomized into the maintenance phase of the study only if all of the following criteria apply:

- Complete a minimum of four cycles of induction therapy, defined as either
  - 4 Phesgo injections + 4 docetaxel infusions

  or
  - 4 Phesgo injections + 12 paclitaxel infusions

  Note: If a participant has received one or two cycles of induction therapy prior to enrollment, these cycles are to be counted towards the required number of cycles for eligibility of the maintenance phase (e.g., if the participant was given one cycle of Phesgo [or trastuzumab SC with pertuzumab IV, or PH IV] +docetaxel prior to enrollment, a minimum of 3 cycles of Phesgo+docetaxel are required prior to entering the maintenance phase)
- Achieve a minimum of SD [or Non-CR/Non-PD for participants with non-measureable disease] (i.e., did not experience PD) according to RECIST v1.1 at the last tumor assessment during the induction therapy phase
- LVEF of ≥50% at the last assessment during the induction therapy phase

In addition, patients should not consume grapefruit, grapefruit juice, grapefruit supplements, or Seville oranges (potent CYP3A inhibitors) within 3 days prior to initiation of giredestrant treatment in Arm B (see Section 5.3.1 and Section 6.8.2).

5.2 EXCLUSION CRITERIA

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

- Previous systemic non-hormonal anti-cancer therapy in the MBC or ABC setting

  Note: Up to one line of single-agent ET given in the metastatic or locally-advanced setting will be allowed.

  One or two cycles of Phesgo (or trastuzumab SC with pertuzumab IV, or PH IV) with docetaxel or paclitaxel in the first line ABC setting is allowed prior to enrollment, provided no limiting toxicities or PD have occurred.
- Prior treatment with a SERD (e.g., fulvestrant)

- Previous treatment with approved or investigative anti-HER2 agents except Phesgo (or trastuzumab SC with pertuzumab IV, or PH IV), *single-agent trastuzumab IV or SC*, ado-trastuzumab emtansine, lapatinib, and neratinib in the neoadjuvant or adjuvant setting
- Disease progression within 6 months of receiving trastuzumab, with or without pertuzumab (IV, SC, or fixed-dose combination), or ado-trastuzumab emtansine in the adjuvant setting
- Non-resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE v5.0 Grade 1 or better (except alopecia, Grade ≤2 peripheral neuropathy, or other toxicities that are not considered a safety risk for the participant per investigator's judgment)
- History of persistent Grade ≥ 2 (NCI-CTC, Version 5.0) hematological toxicity resulting from previous adjuvant or neo-adjuvant therapy
- History of exposure to the following cumulative doses of anthracyclines
  - Doxorubicin >360 mg/m^2
  - Liposomal doxorubicin >500 mg/m^2
  - Epirubicin >720 mg/m^2
  - Mitoxantrone >120 mg/m^2
  - Idarubicin >90 mg/m^2

  If another anthracycline or more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 doxorubicin. (See Appendix 10 for dose conversions).
- Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease

  Participants with a history of CNS metastases or cord compression are eligible if they have been definitively treated with local therapy (e.g., radiotherapy, surgery), are clinically stable, and have not been treated with anticonvulsants or corticosteroids within 2 weeks prior to *enrollment*.
- Dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 7 months after the final dose of Phesgo
  - Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of induction therapy
- Treated with investigational therapy within 28 days prior to initiation of induction therapy
- Treated with localized palliative radiotherapy within 14 days prior to initiation of induction therapy
- Concurrent participation in any other therapeutic clinical trial

- Known hypersensitivity to any of the study medications or to excipients of recombinant human or humanized antibodies
- Current chronic daily treatment (continuous for >3 months) with corticosteroids (dose of 10 mg/day methylprednisolone or equivalent), excluding inhaled steroids
- Poorly controlled hypertension (e.g., systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mmHg)
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, active liver disease including active viral or other hepatitis virus (e.g., hepatitis B or hepatitis C), autoimmune hepatic disorders, or sclerosing cholangitis, current alcohol abuse, or cirrhosis.

  Active viral infection is clinically defined as requiring treatment with antiviral therapy or the presence of positive test results for hepatitis B (hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [anti-HBc]) or HCV antibody. Patients are not required to have HBV, or HCV assessments at screening if these assessments have not been previously performed. Patients that have tested positive for anti-HBc would be eligible if tests for HBsAg and PCR are HBV DNA are negative. Patients who have been cured of their HCV infection (must have an undetectable viral load i.e., a sustained virologic response for 3 months after completing treatment) are eligible to enroll. Patients that have tested positive for the HCV antibody would be eligible if tests for HCV RNA are negative. If the patient is a carrier of HCV and tests positive for HCV RNA, they would not be considered eligible. For patients who have been successfully treated for viral hepatitis, the possibility of re-activation of the virus or reinfection with viral hepatitis should be considered by the Investigator and the overall potential benefits associated with study treatment for the patient should be deemed to exceed the overall risks.

- Active cardiac disease or history of cardiac dysfunction, including any of the following:
  - History or presence of symptomatic bradycardia or resting heart rate <50 beats per minute (BPM) at screening

    Participants on stable dose of a β-blocker or calcium channel antagonist for preexisting baseline conditions (e.g., hypertension) may be eligible if heart rate is at least 50 bpm.
  - History of angina pectoris or myocardial infarction within 12 months prior to study entry
  - History of NCI CTCAE v5.0 Grade ≥3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) ClassII or greater cardiomyopathy
  - QT interval corrected through use of Fridericia's formula (QTcF) >470 ms, 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, including complete left bundle branch block, second- or third-degree heart block, sick sinus syndrome, long QT syndrome, or evidence of prior myocardial infarction
  - 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), 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
  - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second degree AV-block Type 2 [Mobitz 2] or third-degree AV-block)
  - Serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality
  - Clinically significant valvular heart disease
  - Evidence of transmural infarction on ECG
- Major surgical procedure or significant traumatic injury within 14 days prior to enrollment or anticipation of need for major surgery during induction therapy.

  Note: Should surgery be necessary during the study, participants should be allowed to recover for a minimum of 14 days prior to subsequent Phesgo treatment, regardless of the phase of the study (induction therapy or maintenance). Placement of implantable central venous access device (e.g., Port-a-Cath®) is not considered a major surgery.
- Active inflammatory bowel disease, chronic diarrhea, short bowel syndrome, or major upper gastrointestinal surgery, including gastric resection, potentially affecting enteral absorption
- Concurrent, serious, uncontrolled infections, or known infection with HIV with the following exception:

  Individuals who are HIV positive are eligible provided they are stable on anti-retroviral therapy $for \geq 4\ weeks$, have a CD4 count ≥ 350 cells/μL, and have an undetectable viral load and no history of AIDS-defining opportunistic infections within 12 months prior to enrollment.

  Proper taxane dose reduction due to PK interactions with the antiretroviral therapy must be pursued according to local prescribing information.
- Serious COVID-19 infection within 14 days prior to enrollment; however, no screening testing for SARS-CoV-2 is required
- Serious infection requiring oral or IV antibiotics within 7 days prior to screening
- Any serious medical condition or abnormality in clinical laboratory tests that precludes an individual's safe participation in the study

- History of malignancy within 5 years prior to screening, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- For pre- and perimenopausal women: known hypersensitivity to LHRHa, unless willing to undergo bilateral oophorectomy prior to ET initiation that requires ovarian suppression (i.e., experimental arm and AI use in the control arm)
- For all men: known hypersensitivity to LHRHa
- For pre- and perimenopausal women, and men: not willing to undergo and maintain treatment with approved LHRHa therapy for the duration of ET that requires gonadal function suppression (i.e., experimental arm, and AI use in the control arm).
- *Treatment with strong CYP3A4 inhibitors or inducers within 14 days or 5 drug-elimination half-lives, whichever is longer, prior to initiation of giredestrant treatment in Arm B.*

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has the following meal and dietary restrictions:

- *Refrain from consumption of grapefruit or grapefruit juice, grapefruit supplements, or Seville oranges (potent CYP3A enzyme inhibitors) for at least 3 days prior to initiation of giredestrant in Arm B and throughout the maintenance phase.*

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for 1 rescreening opportunity (for a total of 2 screenings per individual) at the investigator's discretion. Individuals are not required to re-sign the consent form if they are re-screened within 28 days after previously signing the consent form. *Assessments with results that previously met the eligibility criteria do not need to be repeated at re-*screening if they still fall within the applicable time windows for screening and baseline. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

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

The investigational medicinal products (IMPs) for this study are Phesgo and giredestrant. Appendix 11 identifies IMPs, non-investigational medicinal products (NIMPs), and auxiliary medicinal products (AxMPs) for this study.

6.1 STUDY TREATMENTS ADMINISTERED

The treatment regimens are summarized in Section 4.1.

If any of the individual study drugs in the induction therapy phase must be delayed or withheld for a day or more (e.g., as per Figure A3-1 for LVEF drop), all agents should be delayed for the same time frame.

If taxane needs to be permanently discontinued in the induction therapy phase prior to reaching at least 4 complete cycles, due to treatment-related toxicity, the participant will discontinue all study treatment and enter follow-up.

If Phesgo is withheld for 3 or more cycles (>9 weeks) or needs to be permanently discontinued for treatment-related toxicity, the participant will be withdrawn from all study treatment and enter follow-up. The participant will be treated as per standard of care at the discretion of the investigator as clinically indicated.

Giredestrant should be permanently discontinued if it is withheld for 3 or more cycles (>9 weeks). If giredestrant is withheld or needs to be permanently discontinued for treatment-related toxicity, the participant should continue to receive treatment with Phesgo alone. If the time between doses of giredestrant is exactly 9 weeks or less then the dosing with giredestrant can be restarted.

If Phesgo needs to be withheld, then giredestrant should also be withheld for the same timeframe.

If the investigator chooses to give ET in Arm A and this needs to be permanently discontinued for treatment-related toxicity, the participant should continue to receive Phesgo alone.

Refer to the schedule of activities (see Section 1.3) for details on follow-up assessments to be performed for participants who discontinue study treatment.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 3.

Table 7 provides a description of assigned study treatments for this study.

Table 7 Study Treatment Description

	Phesgo	Giredestrant
Use	Experimental	Experimental
Drug form	Solution for injection	Capsule
Unit Dose Strength(s)	Loading: pertuzumab 80 mg/mL, trastuzumab 60 mg/mL, rHuPH20 2,000 U/mL Maintenance: pertuzumab 60 mg/mL, trastuzumab 60 mg/mL, rHuPH20 2,000 U/mL	30 mg/capsule
Dosage Level(s)	Loading: pertuzumab 1200 mg trastuzumab 600 mg rHuPH20 30,000 U Maintenance: pertuzumab 600 mg trastuzumab 600 mg rHuPH20 20,000 U Q3W	30 mg QD Day 1–21 of each 21 day cycle
Formulation(s)	Refer to pharmacy manual and/or Investigator's Brochure	Refer to pharmacy manual and/or Investigator's Brochure
Packaging	Loading: 20 mL glass vials Maintenance: 15 mL glass vials	HDPE bottles with a plastic child-resistant cap with induction seal and desiccant
Route of administration	SC injection	Oral
Source	Sponsor	Sponsor

HDPE = high-density polyethylene; Q3W = every 3 weeks; QD =every day.

At applicable sites, during the maintenance phase study treatment may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in mobile nursing (MN) visits and if this is possible per country regulations.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 3.

6.1.1 Phesgo

Phesgo will be provided in single-dose, ready-to-use glass vials and administered subcutaneously as a fixed non–weight-based dose. During the induction therapy phase, Phesgo will be administered prior to taxane-based chemotherapy (i.e., docetaxel or

paclitaxel). If given prior to enrollment, the same taxane used outside the trial should be administered during the induction therapy phase. Participants who experience injection-related symptoms may be pre-medicated with analgesics and antihistamines prior to subsequent injections (see Section 6.8.1).

In the induction therapy phase, a loading dose (1200 mg pertuzumab, 600 mg trastuzumab, 30,000 U rHuPH20) will be administered in the first cycle. In subsequent cycles, maintenance doses (600 mg pertuzumab, 600 mg trastuzumab, 20,000 U rHuPH20) will be administered subcutaneously Q3W. If the patient misses a dose of Phesgo for any cycle and the time between doses is ≥ 6 *weeks but* ≤ 9 *weeks*, a reloading dose of Phesgo (1200 mg pertuzumab, 600 mg trastuzumab, and 30,000 U rHuPH20) should be given. *If the time between doses is* > 9 *weeks, the patient should be discontinued from study treatment (see Section 7.1).*

If a participant was administered one or two doses of Phesgo *(or pertuzumab IV with trastuzumab SC or PH IV)* less than 6 weeks prior to enrollment in the induction phase, Phesgo maintenance dose will be administered. However, if dosing is paused and the time between Phesgo doses is ≥6 weeks but ≤9 weeks, a loading dose should be given. Subsequent maintenance doses will be given Q3W (see Appendix A3–2.3). No dose reductions are allowed for Phesgo.

Phesgo will be administered in accordance with prescribing information. All doses of Phesgo will be administered over 5–8 minutes as a SC injection into the thigh (no other anatomical location is allowed) at a rate of no more than 2 mL/min. Loading dose(s) should be administered over 8 minutes; maintenance doses should be administered over 5 minutes. The injection rate should be adjusted to a rate that is comfortable for the participant. New injections should be given at least 2.5 cm from the previous site and never into areas where the skin is red, bruised, tender, or hard. The entire volume (15 mL volume for the loading dose; 10 mL volume for the maintenance dose) must be injected in one site: splitting the volume into two syringes or injecting at two different sites is not permitted.

After the first loading dose injection, participants will be observed for injection-related symptoms for 30 minutes following the end of the injection. If the participant experiences injection-related symptoms during the injection, the injection should be slowed or interrupted (but may NOT be reduced). If the first injection is well tolerated, participants will be observed for 15 minutes following subsequent injections. Participants may be observed for a longer period at the discretion of the investigator or, if necessary, as per local requirements.

Guidelines for medical management of hypersensitivity/anaphylaxis and administration-related reactions (ARR) are provided in Appendix A3–3.1.1. Clinically significant injection-related symptoms must resolve before taxane-based chemotherapy is started.

6.1.2 Giredestrant

Giredestrant will be supplied as an immediate-release capsule, packaged in high-density polyethylene bottles with a plastic child-resistant cap with induction seal and desiccant. On Days 1–21 of each 21-day cycle during the maintenance treatment phase, participants who have been randomized to Arm B will self-administer one 30-mg giredestrant capsule orally at approximately the same time each day. Giredestrant may be taken with or without a meal.

For cycles where Phesgo is administered in the clinic, the Day 1 dose of giredestrant will be administered in the clinic. For any cycles where Phesgo is administered outside of the clinic (at the participant's home or other suitable location), the Day 1 giredestrant dose may also be administered outside of the clinic. In all cases giredestrant will be administered after the study assessments, as indicated in the schedule of activities (see Section 1.3). If a dose is missed it should be made up, unless the next dose is due within 6 hours. If a dose is vomited, the participant should resume dosing with the next scheduled dose; vomited doses will not be made up.

If giredestrant is withheld or needs to be permanently discontinued for treatment-related toxicity, the participant should continue to receive treatment with Phesgo alone.

6.1.3 Investigator Choice of Taxane

During the induction therapy phase, the investigator's choice of taxane-based chemotherapy (i.e., docetaxel or paclitaxel) will be administered after Phesgo. If a participant received a taxane prior to enrollment, the same taxane used outside the trial should be administered during the induction therapy phase. Refer to the currently approved prescribing information for docetaxel and paclitaxel, as applicable, for formulation, handling, and dosing instructions.

Docetaxel or paclitaxel will be provided by the Sponsor where required by local health authority regulations or may be sourced locally by the site and reimbursed by the Sponsor. Refer to the currently approved prescribing information for docetaxel and paclitaxel, as applicable, for formulation, handling, and dosing instructions. A recommended dosing scheduled is provided in Table 8.

Table 8 Recommended Dosing Schedule for Docetaxel and Paclitaxel

Taxane	Schedule
Docetaxel	Administer 75 mg/m^2 intravenously over 60 (±10) minutes on D1 of each cycle for 4 to 8 cycles (a cycle is 21 days); this dose may be escalated to 100 mg/m^2 if the initial dose was well tolerated.
Paclitaxel	Administer 80 mg/m^2 intravenously over a minimum of 1 hour on D1, D8, D15 of each cycle for 4 to 8 cycles (a cycle is 21 days); this weekly regimen is considered as one complete cycle whenever 3 weekly doses are given.

6.1.4 Optional Endocrine Therapy of Investigator's Choice

The decision to use optional ET must be made prior to randomization and documented in the source notes and recorded in the IxRS. If the decision is to pursue the use of optional ET and the patient is randomized to the control arm, the investigator should prescribe one of the allowed ET options during the maintenance phase. Optional ET allowed in arm A are: tamoxifen or one of the specified third-generation AIs (anastrozole, letrozole, or exemestane). Dose administration of ET should be performed in accordance with the local prescribing information for the respective product.

If the choice of ET needs to be permanently discontinued for treatment-related toxicity, ET must be permanently discontinued and the participant should continue to receive treatment with Phesgo alone. *Switching from one ET to another due to toxicity is not allowed (e.g.,* from anastrozole to tamoxifen).

6.1.5 Luteinizing Hormone–Releasing Hormone Agonist

LHRHa, which may include, but are not limited to, leuprolide acetate, goserelin acetate, or triptorelin pamoate, will be administered to male participants, and pre- and perimenopausal female participants while receiving giredestrant in Arm B. LHRHa may be administered to male and pre- and perimenopausal female participants receiving tamoxifen in Arm A, and should be administered to those receiving an AI in Arm A.

Menopausal status can be re-assessed during the course of the study. For participants for whom stopping LHRHa is considered, serial measurement of FSH and/or estradiol (as per local standard of care) are needed upon withdrawal of LHRH*a, to confirm postmenopausal status.*

The investigator will determine and supply the appropriate LHRHa locally approved for use in BC. LHRHa will be administered according to local prescribing information. Monthly injections are preferred to minimize the potential of exposure to the medication decreasing to sub-therapeutic levels towards the end of the treatment cycle.

If the participant becomes intolerant to current LHRHa, the participant may switch to another approved LHRHa during the study. Bilateral oophorectomy for pre- or perimenopausal women is allowed.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor where required by local regulations. The study site (i.e., investigator or other authorized personnel e.g., pharmacist or mobile nurse) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

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 voice or web-based response system (IxRS)/ by returning the appropriate documentation form 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, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the 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.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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.

Refer to the pharmacy manual and/or Phesgo and giredestrant Investigator's Brochures or local prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

6.3.1 Treatment Assignment

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number from an IxRS. Participants will be enrolled into the induction therapy phase. After completing the induction therapy phase, participants who are eligible to enter the maintenance phase of the study (see Section 5.1.1) will be randomly assigned to treatment Arm A or B. Prior to randomization, investigators must decide and document if optional ET will be prescribed, according to the standard of care. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by disease status, type of metastatic presentation, best OR to induction therapy phase, and intention to give ET of investigator’s choice.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose of Phesgo and giredestrant administered in the clinic or Phesgo administered outside the hospital setting (if applicable) will be recorded in the source documents and recorded on the electronic Case Report Form (eCRF).

When participants self-administer study treatment at home, compliance with study treatment will be assessed.

At the beginning of each patient's study participation, site study staff will provide the patient 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. For giredestrant and any other study drug administered at home, the medication diary, unused study drug, and study drug containers (used or unused) should be collected and reviewed for drug accountability at the beginning of each cycle. Capsules (or tablets, as applicable) that are not returned will be considered to have been taken, unless otherwise specified in the patient's diary/eCRF. Note that dosing eCRFs should be completed using the following prioritization (in the event of discrepancies): 1) site pharmacy drug accountability logs (IMP disbursed minus IMP returned); 2) patient daily dosing diary; and 3) clinic visit patient interview notes.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Appendix 2.

6.5 DOSE MODIFICATION

Modification of the Phesgo and giredestrant dose(s) is not permitted. Modification of the taxane dose will be as per standard of care.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer continued access to Roche IMPs (Phesgo±giredestrant) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to IMP, as outlined below.

A participant will be eligible to receive Roche IMPs (Phesgo±giredestrant) after completing the study if all of the following conditions are met:

- *The participant has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.*
- *There are no appropriate alternative treatments available to the participant.*

- *The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.*

A participant will not be eligible to receive Roche IMPs (Phesgo±giredestrant) after completing the study if any of the following conditions are met:

- *The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).*
- *The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for HER2+/ER+ breast cancer.*
- *The Sponsor has reasonable safety concerns regarding the IMP as a treatment for HER2+/ER+ breast cancer.*
- *Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country.*

The Roche Global Policy on Continued Access to IMP is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF 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 adverse events, should be reported as described in A2–7.12.

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.

6.8 CONCOMITANT THERAPY

Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol–mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit must be recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions regarding concomitant or prior therapy.

6.8.1 Permitted Therapy

Use of the following concomitant therapies is permitted as described below:

- Acceptable methods of contraception must be used when the female participant or male partner is not surgically sterilized or does not meet the study definition of postmenopausal (≥12 months of amenorrhea). See Section 5.2 for the permitted methods of contraception.
- Gonadotropin-releasing hormone agonists for fertility preservation.
- Vitamin and mineral supplements.
- Cardiovascular medications: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers and diuretics (for treatment of arterial hypertension with a goal to reduce blood pressure <140/90mmHg), beta blockers, calcium channel blockers and digoxin (for heart rate control), thrombocyte aggregation inhibitors
  - See Section 6.8.4 for cautionary therapy for participants receiving giredestrant
- Paracetamol (acetaminophen) or other analgesics, and diphenhydramine, chlorpheniramine, or other antihistamines can be used according to local clinical practice for the prevention and treatment of ARRs associated with Phesgo.
- Symptomatic anti-emetics, anti-diarrheal therapy, and other palliative and supportive care for disease-related symptoms may be administered at the investigator's discretion.
- Pain medications administered per standard clinical practice are acceptable while the participant is enrolled in the study and are to be recorded on the Concomitant Medications eCRF.
- Steroids, antihistamines, and anti-emetics for docetaxel or paclitaxel premedication according to routine practice at each clinical site
  - Short-term use of corticosteroids to treat or prevent allergic or infusion reactions are allowed, however, the dose must not exceed >20 mg/day of dexamethasone (or equivalent) for >7 consecutive days.
- Bone sparing agents (e.g., bisphosphonates, denosumab) may be given according to their product license and routine clinical practice, at the investigator's discretion
- Blood transfusions at the investigator's discretion
- Standard therapies for preexisting medical conditions and medical or surgical complications
- Regulatory-approved or authorized under emergency use authorization (EUA) COVID-19 vaccines are permitted, and should be treated as concomitant medications. If a COVID-19 vaccine is given, report the product or brand/trade or company manufacturer if available (Examples: Pfizer Covid-19 vaccine, Moderna Covid-19 vaccine). If not available, report as Covid-19 vaccine. Record each dose separately.
- Any other medication not included in the list of prohibited medications.

In general, investigators should manage a participant's care with supportive therapies as clinically indicated, per institutional standard practice. Participants who experience infusion/injection-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per institutional standard practice. Serious infusion/injection-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  After the induction therapy phase, palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

- Radiotherapy to the brain as outlined below:

  Participants whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided <u>all</u> of the following criteria are met:

  – The participant has no evidence of progression or hemorrhage after completion of CNS-directed therapy.

  – The participant has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Participants who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  – Participants experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment after Medical Monitor consultation has been performed. Participants who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

6.8.2 <u>Prohibited Therapy</u>

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

- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy [fulvestrant included], immunotherapy,

radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 5.2), and during study treatment, until disease progression is documented and the participant has discontinued study treatment, with the exception of palliative radiotherapy, radiotherapy to the brain, and local therapy under certain circumstances (see Section 6.8.1 for details).

- Regular systemic treatment with steroids

  Short-term corticosteroids to treat and prevent allergic or infusion reactions are allowed; however, the dose must not exceed > 20 mg/day of dexamethasone (or equivalent) for >7 consecutive days.

- Tumor necrosis factor-α inhibitors
- Anti-T cell antibodies
- Any systemically active oral, injected, or implanted hormonal method of contraception except for progesterone coated IUDs that had been previously implanted
- Hormone-replacement therapy
- *Preliminary data from Study GP44001 showed that itraconazole, a strong CYP3A inhibitor, increased giredestrant exposure to approximately 3.98-fold. Carbamazepine, a strong CYP3A inducer, decreased giredestrant exposure by approximately 75%. These results suggest that giredestrant is a moderately sensitive CYP3A substrate. Co-administration of giredestrant with the following concomitant therapies should be avoided:*
  - *Strong CYP3A inhibitors, including, but not limited to, the following: atazanavir, ritonavir, lopinavir, telaprevir, telithomycin, indinavir, nelfinavir, saquinavir, clarithromycin, troleandomycin, itraconazole, ketoconazole, voriconazole, posaconazole, nefazodone, mibefradil*
  - *Strong CYP3A inducers, including, but not limited to, the following: apalutamide rifampin, carbamazepine, phenytoin, enzalutamide, lumacaftor, and hyperforin (St. John's Wort).*

    The above lists of CYP3A concomitant medications are not necessarily comprehensive. Thus, the investigator should consult local prescribing information for any concomitant medication as well as the internet reference provided below when determining whether a certain medication strongly inhibits or induces CYP3A. If the benefit from the use of a strong CYP3A inhibitor or strong CYP3A inducer outweighs the risk and no suitable alternative is available, a strong CYP3A inhibitor or strong CYP3A inducer may be used for a short period of up to 2 weeks. Giredestrant should be withheld during the use of a strong CYP3A inhibitor (e.g., before initiating and during the 5-day COVID-19 treatment with PAXLOVID™ [containing the strong CYP3A inhibitor ritonavir]) (FDA 2022).

Enrolled/randomized participants who subsequently require the use of any prohibited therapies must be discontinued from study treatment as outlined in Section 7.1.

6.8.3 Cautionary Therapy

For guidelines on cautionary therapy for participants receiving investigator's choice of ET (control arm) or taxane, refer to the local prescribing information for the respective product.

6.8.3.1 Herbal Therapies

Concomitant use of herbal therapies including traditional Chinese medicines are not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 6.8.2) may be used during the study at the discretion of the investigator.

6.8.3.2 Surgery

Participants who require surgery as part of medical treatment in the absence of disease progression must exercise caution, and Phesgo should be temporarily held for at least 14 days prior to major elective surgery. After the temporary treatment hold is complete, Phesgo may be re-initiated based upon a clinical assessment of satisfactory wound healing and recovery from surgery.

6.8.4 Cautionary Therapy for Participants Receiving Giredestrant

6.8.4.1 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. Participants on 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.

6.8.4.2 Surgery

Participants who require surgery as part of medical treatment in the absence of disease progression must exercise caution, and giredestrant should be temporarily held for at least 7 days prior to major elective surgery. After the temporary treatment hold is complete, giredestrant may be re-initiated based upon a clinical assessment of satisfactory wound healing and recovery from surgery.

6.8.4.3 *Moderate CYP3A Inducers*

Where possible and feasible, investigators should consider alternatives to the concomitant administration of moderate CYP3A inducers with giredestrant. 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).

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) all study treatment (Table A3-1 provides discontinuation guidelines for giredestrant only). If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. Refer to the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue all study treatment if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to RECIST v1.1. Exception to this is isolated CNS progression treated with local therapy (e.g. radiosurgery, neurosurgery) whereupon the investigator judges the participant to still be benefiting systemically from study treatment (i.e., sustaining a systemic response and good clinical status despite CNS progression, and able to resume study treatment within 9 weeks of the last dose of maintenance Phesgo [*Section 6.1*]). These participants may still continue study treatment, although they will be counted as having a PFS event at time of CNS progression while still being evaluable for OS.
- Persistent non-compliance with protocol-specified drug administration and follow-up tests
- Heart failure (NYHA Class III and IV)
- A confirmed significant LVEF decrease ≥10 percentage points from baseline and to an LVEF value of below 50% (see Figure A3-1). Confirmation should be completed within approximately 3 weeks
- Anaphylaxis (participants must discontinue the relevant study drug if it is clear which drug was responsible. If Phesgo is deemed responsible, then the participant must discontinue all study treatment). Participants who experience any of the following events will be discontinued from study treatment:
  - Grade 4 allergic reaction

  - Grade 3 or 4 hypersensitivity reaction
  - ARDS
  - Bronchospasm
- Withholding Phesgo for 3 or more cycles (>9 weeks) or permanently discontinuing for treatment-related toxicity (see A3–2.3)
- Unable to tolerate the assigned taxane and discontinue prior completing the minimum of four cycles in the induction therapy phase

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants will return to the clinic for a treatment discontinuation visit 28 (± 3) days after the final dose of study drug.

After treatment discontinuation, information on survival status and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death (unless the participant withdraws consent or the Sponsor terminates the study). If a participant requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Refer to the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

If a participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., complete blood count) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures and local HER2 and ER/PgR status), reproductive status (including menopausal status), and smoking history will be recorded at baseline. Any medication and/or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded at baseline. Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

At applicable sites, certain study assessments may be performed by a MN professional at the participant's home or another suitable location to improve access and convenience for participants participating in the study. The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Section 1.3) will specify the assessments that may be performed by an MN professional.

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Participants will undergo tumor assessments at screening, at Week 9 (*weeks counted from administration of first induction therapy, on or off study, whichever is earlier)* to ensure at least one evaluation is conducted during the induction therapy phase), then every 12 weeks up to 36 months then every 18 weeks thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1. A window of ±7 days will be given for each assessment. Tumor assessments should be scheduled relative to the date of first induction therapy (either on study or prior to entry) than the date of the previous tumor assessment. Tumor assessments are to continue according to schedule in participants who discontinue treatment for reasons other than disease progression, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Tumor assessments performed as the standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet the criteria outlined below.

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of physical examinations, CT scans, MRI scans, and bone scans, according to RECIST v1.1 (see Appendix 7).

CT scans should include chest, abdomen, and pelvic scans; CT scans of any other sites of disease should be included if clinically indicated. The CT scans, including a brain CT scan (when clinically indicated), should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT, without contrast, or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease.

Clinical assessment of superficial disease must coincide with the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the eCRF.

Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions. Abnormalities identified on bone scans must be confirmed by X-ray, CT scan with bone windows, or MRI scan. Special considerations regarding the measurability of bone lesions are outlined in RECIST v1.1 (see Appendix 7).

To ensure a valid comparison of tumor data and uniformity in the assessment of tumor response during the study, the following procedures should be implemented at the study site:

- All lesions identified at baseline (target and non-target) will be re-assessed using the same imaging method throughout the course of the study. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Whenever possible, assessments should be performed by the same evaluator to ensure internal consistency across visits.
- All CT scans, bone scans (from participants with bone metastases), and other relevant imaging such as MRIs obtained for all participants enrolled at the study site should be reviewed by the local radiologist who, together with the investigator, will determine the local assessment of response and progression.
- Images for all tumor assessments will be prospectively collected to enable a retrospective BICR.

8.1.1.1 Radiographic Assessments

Baseline (prior to enrollment or first off-study induction therapy)

Baseline tumor assessment should be performed within 28 days of enrollment or start of off-study induction therapy (unless otherwise specified) and will include the following assessments:

- CT or MRI scan of the chest, abdomen, and pelvis
- CT or MRI scan of brain, in participants with previously treated brain lesions; the scan must be within the screening window and ≥4 weeks after the completion of radiotherapy. For all other participants, brain scans should be acquired if clinically indicated.
- CT or MRI scan of any other sites of disease, as clinically indicated
- Clinical assessment of superficial disease, including photographs of all superficial metastatic lesions
- Bone scans or other institutional standard bone imaging *(e.g., PET scan with FDG, bone scintigraphy with technetium)*

Radiographic tumor assessments and bone scans performed as routine procedures before the signing of the Informed Consent Form may be accepted as baseline assessments provided the following criteria are met:

- The tests were performed per the method requirements outlined above
- Appropriate documentation indicating that these radiographic tumor assessments were performed as the standard of care is available in the participant's source notes
- Bone scans were performed within 6 weeks prior to enrollment or start of off-study induction therapy

Postbaseline

The following postbaseline tumor assessments will be performed:

- CT or MRI scan of the chest, abdomen, and pelvis
- CT or MRI scan of brain, if disease was present at baseline or if clinically indicated
- CT or MRI scan of any other sites of disease identified at baseline
- Clinical assessment of sites of superficial disease identified at baseline
- For participants who have bone lesions at baseline:
  - X-ray, CT scan, or MRI scan of selected evaluable bone lesions, ensuring consistent use of the same modality for all evaluations

    Note: Bone scans *or other institutional standard bone imaging* are required to confirm CR; however, areas that have received palliative radiotherapy during the study cannot be used to assess response to study treatment.

    Postbaseline bone scans or other institutional standard bone imaging for participants who have bone lesions at baseline will be performed at every second tumor evaluation (i.e., at 21 weeks after first induction therapy then every 24 weeks (± 7 days) for the first three years and every 36 weeks (± 7 days) thereafter) or as clinically indicated.

For participants with symptomatic deterioration, every effort should be made to provide documented progression via radiographic modality.

Details regarding imaging procedures will be provided in an imaging manual.

Radiographic images will be submitted to an IRC for a quality and completeness check, for central review, and for temporary storage prior to transferring images to the Sponsor.

Radiographic images, whether reviewed locally or centrally, must be evaluated by a qualified, certified expert.

8.1.1.2 Response Evaluation

Objective response will be determined by the investigator at specified timepoints according to RECIST v1.1 (see Appendix 7). Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

Endpoints (e.g., PFS, OS, ORR, DOR, CBR) will be calculated programmatically by the Sponsor on the basis of investigator assessments of response at each specified timepoint.

8.1.2 Clinical Outcome Assessments

PRO instruments will be completed to assess the treatment benefit of Phesgo and giredestrant from the participant's perspective.

PRO data will be collected from participants randomized to receive study maintenance treatment through use of the following instruments: European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life–Core 30 Questionnaire (QLQ-C30) (Appendix A5–1.1), EORTC Quality of Life–BR23 Questionnaire (QLQ-BR23) (Appendix A5–1.2), the worst pain item from the Brief Pain Inventory-Short Form (BPI-SF) (Appendix A5–1.3), select items of the PRO-CTCAE (Appendix A5–1.4), the GP5 overall treatment side-effect bother item of the *Functional Assessment of Cancer Therapy–General* (FACT-G) (Appendix A5–1.5), the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) (Appendix A5–1.6), and the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) (Appendix A5–1.7) (assessed in that order).

The questionnaires will be completed in their entirety by the participant at baseline (Cycle 1, Day 1 of maintenance therapy) and at subsequent timepoints as noted in Table 2–Table 4. To minimize burden on participants, after treatment discontinuation for any reason and regardless of receipt of subsequent anti-cancer therapy, only the EORTC QLQ-C30, as well as single-items GP5 from the FACT-G and the pain item from the BPI-SF, and the EQ-5D-5L measure may be administered over the telephone to participants or completed at the clinic during follow-up visits. Instructions and telephone scripts for administering the PRO assessments via telephone interviews (during the post-treatment follow-up period of the study) will be provided when available in the local language.

8.1.2.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in pre-printed booklets to enable the appropriate instruments to be administered in the correct order at each specified timepoint during the study (see Table 2–Table 4). The booklets will be labeled with the timepoint of administration. At the clinic during the maintenance treatment phase, instruments will be self-administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments (exceptions can be made where this is not feasible, e.g., non-PRO assessments conducted at a different location, provided results are not conveyed to participants to avoid bias), and prior to the administration of study treatment. If participants receive Phesgo at home, the mobile nurse will provide the patient with the PRO questionnaires for completion at their home on their scheduled visit date.

In the event that after completion of the PROs at the start of a treatment cycle it is determined that the dose of Phesgo or giredestrant should be delayed, the Day 1 PROs will not be re-administered when the participant returns to the clinic for treatment following the delay. For example, PROs will be completed at the planned Day 1 of Cycle 2 visit prior to the actual office visit. In the event that the review of clinical laboratory results and adverse events demonstrates that Phesgo or giredestrant should not be resumed at this visit, the actual Day 1 of Cycle 2 visit will not occur until the

participant is fit to resume dosing. The PROs will not be repeated at the delayed Day 1 of Cycle 2 visit when dosing resumes.

For participants who are unable to complete the measures on their own, interviewer assessment is allowed but can only be conducted by a member of the clinic staff who reads the questionnaire items to the participant verbatim; no interpretation, rephrasing, or rewording of the questions is allowed during interview-assisted completion.

During clinic/home visits, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments.
- Site staff/MN must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Site staff/MN should allow sufficient time for participants to complete the instruments, estimated to be 15–25 minutes at specified visits.
- Site staff/MN should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff/MN should not interpret or explain questions, but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff/MN should review all completed instruments and should ask the participants to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff/MN should ask the participants to complete the item or confirm that the item was intentionally left blank.
- Hard copy originals of the questionnaires must be maintained as part of the participant's medical record at the site for source data verification. These originals should have the study participant number and date, and time of completion recorded in compliance with good clinical practice.
- Sites will enter participant responses to the PRO questionnaires into the electronic data capture (EDC) system.

8.1.2.2 EORTC QLQ-C30

The QLQ-C30 is a validated, reliable self-reported measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Appendix A5–1.1). It consists of 30 questions that assess five aspects of participant functioning (physical, emotional, role, cognitive, and social), three symptom scales (Fatigue, Nausea and Vomiting, and Pain), global health status and quality of life (QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms

items are scored on a 4-point scale that ranges from "not at all" to "very much," and the global health status and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The QLQ-C30 module takes approximately 10 minutes to complete.

8.1.2.3 EORTC QLQ-BR23

The EORTC QLQ-BR23 breast cancer module is meant for use among participants diagnosed with BC (Sprangers et al. 1996) (see Appendix A5–1.2). It incorporates five multiple-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image, and sexual functioning with a recall period of the previous week. In addition, single items assess sexual enjoyment, hair loss, and future perspective. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much." The QLQ-BR23 module takes approximately 7 minutes to complete. Since the QLQ-BR23 was not originally developed or tested and validated with men, male participants in this study will not complete the QLQ-BR23 questionnaire.

8.1.2.4 BPI-SF Worst Pain Item

Cancer-related pain severity will be assessed using the BPI-SF worst pain item (see Appendix A5–1.3), a *patient-reported* measure rated on a 10-point numeric rating scale, with 0 meaning “no pain” and 10 indicating “worst pain you can imagine”, with a 24-hour recall period. This assessment approach follows consensus recommendations for measuring pain in clinical trials and is commonly used as a standalone item across diseases (including BC), therapies, and languages (Dworkin et al. 2005, Harrington et al. 2014). The BPI-SF takes less than 1 minute to complete.

8.1.2.5 WPAI:GH

The WPAI:GH v2.0 is a validated questionnaire that is used to assess occupational work productivity and activity impairment (Reilly et al. 1993) (see Appendix A5–1.6). The WPAI:GH consists of 6 questions about the effects of BC on the following in the past 7 days: employment status; hours missed due to health problems; hours missed due to other reasons; hours actually worked; and two questions that measure the degree to which health problems affected productivity while working (presenteeism) and regular daily activities, scored on a 0−100 scale. The WPAI: GH takes approximately 3 minutes to complete.

8.1.2.6 EuroQol EQ-5D-5L

The EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix A5–1.7). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analog Scale that measures health state. The EQ-5D-5L is designed to capture a participant's current health status. Published weighting systems allow for creation of a single composite score of the participant's

health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose and throat, cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities beyond expected variation or normal age-related changes should be recorded as adverse events on the Adverse Event eCRF. Limited physical examinations may be performed by an MN professional as outlined in Section 1.3.

8.2.2 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Vital sign measurement may be performed by an MN professional as outlined in Section 1.3.

8.2.3 ECOG Performance Status

Performance status will be completed at screening and as specified in the schedule of activities (see Section 1.3) using the ECOG performance status scale (see Appendix 8) and recorded on the eCRF. ECOG performance status assessment may be performed by an MN professional as outlined in Section 1.3.

8.2.4 Cardiac Function

Participants must be assessed for a history of cardiac events, including, a physical examination, LVEF assessment, and a baseline ECG prior to enrollment to exclude any cardiac condition that would render them ineligible for participation in this trial. Cardiac function will be assessed locally according to the schedule of activities (see Section 1.3). ECG, ECHO, and MUGA scan reports are considered source documents and should be retained in the participant's medical records.

See Figure A3-1 for the treatment algorithm based on LVEF values, Appendix A3–3.1.2 for management guidelines, and Section 8.3.8.2 for reporting guidelines of adverse events of heart failure and asymptomatic decline in LVEF.

8.2.4.1 LVEF Assessment

All participants must have a LVEF measurement of at least 50% by ECHO (preferably) or MUGA scan prior to enrollment. The same method (ECHO or MUGA) used at screening should be used throughout the study for the participant to the extent possible, and should be obtained at the same institution. Investigators must be aware of local institutional regulations regarding the maximum allowable frequency of repeat MUGA scans. The repeated administration of radioisotopes is limited in some nuclear medicine laboratories, and participants in this study require monitoring on more than four occasions within 1 year.

ECHO or MUGA reports must be reviewed and acted upon as soon as available; however, assuming a participant does not have cardiac symptoms, study procedures may continue while the results are confirmed.

Participants who discontinue study treatment for heart failure or LVEF decline should continue to undergo LVEF assessments according to the schedule of activities in Section 1.3 (irrespective of the initiation of alternative systemic anti-cancer therapy) until resolution, improvement to baseline status, no further improvement can be expected, or death.

8.2.4.2 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS interval, QT interval, and QT interval corrected through use of Fridericia's formula (QTcF).

A single *12-lead* ECG will be performed and clinically significant abnormalities will be confirmed by triplicate reading.

Lead placement should be as consistent as possible. ECGs for each participant should be obtained from the same machine wherever possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. 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, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent

study file at the site. The following should be recorded on the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

8.2.5 Clinical Safety Laboratory Tests

See Appendix 6 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event Case Report Form (CRF) (see Appendix 2).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days (± 3 days) of the final dose of Phesgo should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Sample collection may be performed by an MN professional as outlined in Section 1.3.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.6 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 6. Pregnancy testing may be performed by an MN professional as outlined in Section 1.3.

8.2.7 Clinical Outcome Assessments

PRO instruments will be completed to assess the treatment benefit of Phesgo and giredestrant from the participant's perspective. In addition, PRO instruments will enable the capture of each participant's direct experience with Phesgo and giredestrant.

PRO exploratory safety data will be collected from participants randomized to receive study maintenance treatment through use of the following instruments: select items of

the PRO-CTCAE (Appendix A5–1.4), and the GP5 overall treatment side-effect bother item of the FACT-G (Appendix A5–1.5).

Refer to Section 8.1.2 for description of order of assessments and description of data collection methods.

8.2.7.1 PRO-CTCAE

The PRO-CTCAE is a validated item library that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 participant-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days.

A subset of seven symptoms (nausea, vomiting, diarrhea, rash, joint pain, fatigue, hot flashes), deemed most applicable to the current study treatments has been selected for this study (see Appendix A5–1.4). Symptoms have been selected on the basis of being self-reportable, having a symptomatic equivalent in the PRO-CTCAE item library, and being salient to participants' experience with Phesgo and/or giredestrant on the basis of preliminary safety data for giredestrant and published safety data for Phesgo and common endocrine therapies. Participants will also be asked to report any other symptoms they are experiencing in an open text field item.

8.2.7.2 FACT-G Single-Item GP

The FACT-G instrument, Version 4 (see Appendix A5–1.5) is a validated and reliable 27-item questionnaire comprised of four subscales that measure physical (7 items), social/family (7 items), emotional (6 items), and functional well-being (7 items), and is considered appropriate for use with participants with any form of cancer (Cella et al. 1993; Webster et al. 1999). In this study, the single-item GP5 (“I am bothered by side effects of treatment”) from the physical well-being subscale of the FACT-G has been selected for individual item analysis to document the level of bother of symptoms on participant’s lives. Participants will assess how true the statement “I am bothered by side effects of treatment” has been for them in the previous 7 days on a 5-point scale (0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; 4, very much). The single-item GP5 from the FACT-G takes less than a minute to complete.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 2.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7.1).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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 (see Appendix A2–5). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 28 days after the final dose of Phesgo at the timepoints specified in the schedule of activities (see Section 1.3). After this period, only drug-related serious adverse events, heart failure (irrespective of causal relationship and for up to 3 years after Phesgo discontinuation) and pregnancies (up to 7 months after Phesgo discontinuation), should continue to be collected (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in A2–4. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 2.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Phesgo	Phesgo Investigator's Brochure
Giredestrant	Giredestrant Investigator’s Brochure

The Sponsor 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.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 7 months after the final dose of Phesgo.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 7 months| after the final dose of Phesgo.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 4. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 2.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest and Selected Adverse Events

8.3.8.1 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A2–3.1 for reporting instructions). Adverse events of special interest for this study 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 Section A2–7.7)

- Suspected transmission of an infectious agent by a 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 participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

- An asymptomatic decline in LVEF that requires treatment or that leads to discontinuation of Phesgo must be reported in an expedited manner with use of the Serious Adverse Event Form and classifying the event as an Event of Special Interest that is immediately reportable
- 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 event

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 3.

8.3.8.2 Selected Adverse Events

Additional data will be collected for the following selected adverse events

- Administration-Related Reactions: Injection-Related Reactions and Injection Site Reactions (See Appendix A2–7.1 for recording procedures and Appendix 3 for management guidelines)
- Asymptomatic Declines in Left Ventricular Ejection Fraction (See Appendix A2–7.14 for recording procedures and Appendix Appendix 3 for management guidelines)
- Heart Failure (See Appendix A2–7.14 for recording procedures and Appendix Appendix 3 for management guidelines)

8.3.9 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours a day 7 days a week. Details will be available separately.

8.4 PHARMACOKINETICS

Blood samples will be collected for measurement of plasma concentrations of giredestrant and serum concentrations of pertuzumab and trastuzumab (within Phesgo) as specified in the schedule of activities (see Section 1.3).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of giredestrant, pertuzumab, and trastuzumab. Samples collected for analyses of giredestrant, pertuzumab, and trastuzumab concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.

PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

8.5 PHARMACODYNAMICS

Pharmacodynamic biomarker assessments will not be performed in this study.

8.6 GENETICS

Refer to Section 8.7 and Appendix 9 for information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Blood and plasma samples for exploratory research on biomarkers
- Archival tumor tissue samples from primary (preferred) and/or metastatic sites obtained during screening for confirmation of HER2 positivity, for retrospective ER and PgR status assessment, and for further research on exploratory biomarkers.

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections must be submitted prior to study enrollment. In exceptional circumstances, 11–19 slides are acceptable provided that other eligibility requirements are met (see Section 5); however, a minimum of 20 slides is highly preferred. For China, the number of slides required for eligibility will be based on HGRAC specifications.

  Tumor tissue should be of good quality, as determined on the basis of total and viable tumor content and must have been evaluated for HER2 expression prior to enrollment. Local ER positivity should be preferentially assessed on the same lesion. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (*highly recommended with at least* three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and

yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, bone metastases, and lavage samples are not acceptable.

For participants with bilateral BC (synchronous or developed at a later stage), or multicentric (multiple tumors involving more than one quadrant) BC, HER2 positivity must be centrally determined in a metastatic biopsy or at least in one lesion if assessed on the primary tumors. If multiple samples are submitted, the highest HER2 level will be taken into consideration.

If multiple tumor specimens collected at different timepoints are submitted (e.g., an archival specimen [from initial BC diagnosis] and tissue from metastatic or locally-advance BC disease), the HER2 status will be first assessed on the primary tumor or less recent tumor specimen for the purpose of determining eligibility.

If both primary and metastatic tumor tissues are submitted, in addition to HER2 testing, both samples may be used for exploratory purposes to analyze any changes in biomarkers during the participant's treatment journey.

If the submitted tumor tissue is determined to be unsuitable or insufficient for required testing, an additional pretreatment tumor sample is required, but only if the benefit of such investigations are deemed to outweigh any risk in the judgment of the investigator.

- Tumor tissue sample obtained at the time of progression, if deemed clinically feasible, for exploratory research on biomarkers

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections should be submitted at the time of disease progression

  Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner.

  Samples collected by means of resection, core-needle biopsy at least three cores preferred, or excisional, incisional, punch, or forceps biopsy are preferred.

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.10.

Exploratory biomarker research can be performed on tissue and liquid samples and may include, but will not be limited to, analysis of biomarkers or genes or gene signatures associated with the HER2 and ER/PgR pathways and the classification of the PAM50 subtypes or ctDNA to assess BC biology or treatment effects or disease progression. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes.

NGS methods may include WGS or WES of tissue and blood samples. Genomic research will focus on somatic variants. DNA extracted from blood may be compared with DNA extracted from tissue to distinguish somatic variants from germline variants.

For sites in China, collection and submission of blood and plasma samples and tumor tissue for exploratory biomarker analyses and assay development are contingent on the approval of the exploratory research by the IRB or EC and, if applicable, an appropriate regulatory body. The collection of samples for exploratory analyses in China may be restricted to accommodate local regulations and requirements

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 5). Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.10.2) biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the following exceptions:

- For enrolled participants, remaining archival tissue blocks will be returned to the site upon request or no later than completion of the final Clinical Study Report, whichever occurs first. For individuals who are not enrolled, remaining archival tissue blocks will be returned to the site no later than *3 months* after eligibility determination.

Data generated from samples collected for exploratory biomarker research will be analyzed in aggregate rather than on an individual basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants. In addition, given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Antibodies to pertuzumab, trastuzumab, and rHuPH20 will be evaluated in plasma and serum samples collected from all participants *in the induction therapy phase, and in participants in A*rm B during the maintenance therapy phase according to the schedule of assessments. Additionally, plasma and serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum and plasma samples will be screened for antibodies binding to pertuzumab, trastuzumab, and rHuPH20 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to pertuzumab, trastuzumab, and rHuPH20 and/or further characterize the immunogenicity of pertuzumab, trastuzumab, and rHuPH20.

The detection and characterization of antibodies to pertuzumab, trastuzumab, and rHuPH20 will be performed through use of a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for pertuzumab and trastuzumab serum concentrations to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment. Samples may be stored for a maximum of 5 years (or according to local regulations) after the final Clinical Study Report has been completed at a facility selected by the Sponsor to enable further analysis of immune responses to pertuzumab, trastuzumab, and rHuPH20.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.10.1 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Participants at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with acquired resistance to study treatment are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research may include exploration of germline variants.

The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 8.10.1) will not be applicable at that site. These WGS/WES samples are not applicable for China.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which participants are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual participant basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Appendix 1).

8.10.2 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.10.2.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. Samples for the RBR will not be collected in China. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.10.2.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10.2) will not be applicable at that site.

8.10.2.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to Phesgo and giredestrant, diseases, or drug safety:

- Blood samples collected at timepoints specified in the schedule of activities (Section 1.3, Table 5)
- Leftover blood, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger

dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.10.2.4 Data Protection, Use, and Sharing

RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual participant basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.10.2.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.10.2.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.10.2.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate

parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1 STATISTICAL HYPOTHESES

The primary analysis will be a comparison of the investigator-assessed PFS (after randomization following induction therapy) between the two treatment arms using a stratified log-rank test at an overall 0.05 significance level (two-sided).

The statistical hypothesis of this study is as follows:

- H_0: PFS (Arm A) = PFS (Arm B)
- H_1: PFS (Arm A) ≠ PFS (Arm B)

PFS (Arm A) represents the progression-free survival function in the Phesgo (control) arm and PFS (Arm B) represents the progression-free survival function in the Phesgo plus giredestrant (experimental) arm.

The null and alternative hypotheses will be tested at a two-sided 0.05 significance level. The primary trial objective is to demonstrate superiority of the experimental over the control treatment.

9.2 SAMPLE SIZE DETERMINATION

Given that up to 10% of participants may experience PD, limiting toxicity, or withdraw consent, in order for 730 participants to be randomized, up to 812 participants will be enrolled in the induction phase. Approximately 730 participants (following induction therapy) will be randomized in a 1:1 ratio to receive either Phesgo plus giredestrant (experimental arm) or Phesgo (control arm). The sample size is determined by the primary endpoint, investigator-assessed PFS, comparing the two treatment arms.

The primary analysis of PFS will be conducted when approximately 380 PFS events are observed in the study. The study is designed with 80% power at the 5% (two-sided) level of significance to detect HR of 0.75, which corresponds to an improvement in median PFS from 20 months to approximately 26.7 months. The largest HR determined to be statistically significant at the 5% level will be approximately 0.818, which corresponds to median improvement in PFS from 20 to 24.5 months.

The enrollment duration for 730 participants is projected to be approximately 36 months after *randomization* of the first participant. For both the experimental and control arms,

an annual loss to follow-up rate of 5% is assumed. On that basis, it is projected that the primary PFS analysis will occur approximately 50 months after the first participant is *randomized*.

OS will be tested in a hierarchical approach i.e., only if PFS is statistically significant at the primary analysis. Overall the study will incorporate three OS analyses; two interim and the final analysis. The first OS interim analysis will be at PFS primary analysis with projected ~163 deaths, the second OS interim analysis with projected ~298 deaths at ~84 months after the first participant is randomized, and the final OS analysis with projected ~387 deaths (which will provide 80% power to detect a 25% improvement in OS, with an assumed median OS in the control arm of 60 months) at ~122 months after the first participant is randomized. The Lan-DeMets implementation of the O'Brien and Fleming alpha-spending function will be used to control the overall type I error for the OS comparison at a two-sided 0.05 significance level. See Section 9.5 for detail assumptions and characteristics of the interim and final analyses for OS.

9.3 ANALYSIS SETS

The following populations are defined:

Participant Analysis Set	Description
Full Analysis Set	All participants assigned to treatment groups as randomized in the maintenance phase by the IxRS.
Safety Evaluable Combined Phase	All participants enrolled in the study and who take at least one dose of study treatment. Participants in the maintenance phase will be analyzed according to the treatment they actually received.
Safety Evaluable	All participants randomly assigned to study treatment in the maintenance phase and who take at least one dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK Evaluable	All participants randomly assigned to study treatment in the maintenance phase and who receive at least one dose of study treatment *in Arm B*. Participants who have at least one evaluable serum pertuzumab and trastuzumab concentration *and at least one evaluable plasma giredestrant concentration* in Arm B.
ADA Evaluable	All randomized participants *in Arm B* in the maintenance phase who have at least one ADA assessment.

ADA= anti-drug antibody; PK=pharmacokinetic.

9.4 STATISTICAL ANALYSES

The Statistical Analysis Plan will be finalized prior to the CCOD and include a more technical and detailed description of the statistical analyses described in this section.

This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1 General Considerations

All efficacy analyses will be performed on the full analysis set population, unless otherwise specified. All safety analyses will be performed in the safety evaluable population, unless otherwise specified.

Analyses of demographics and other baseline information will be based on the full analysis set population. The baseline value of any variable will be defined as the last available data point prior to the first administration of study drug in the maintenance phase.

9.4.2 Primary Endpoint

The primary comparison of interest is the HR of investigator-assessed PFS defined in Table 6. The primary trial objective is to demonstrate superiority of the Phesgo plus giredestrant arm over the Phesgo arm.

9.4.3 Primary Estimand

Following the estimand framework introduced in the ICH-E9 addendum (ICH 2020), the attributes of the estimand built around the primary endpoint are defined as follows:

- **Population:** 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 and completed induction therapy with Phesgo+Taxane, as defined in the inclusion and exclusion criteria (see Section 5)
- **Variable:** PFS, defined as time after 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
- **Treatment**: Phesgo plus giredestrant (experimental arm) or Phesgo (control arm). During the conduct of the study (participants may also receive concomitant medications as detailed in Section 6.8.)
- **Intercurrent events (IE) and handling strategy:**
  - Use of any non-protocol anti-cancer treatment (NPT), as detailed in Section 6.8.2, prior to disease prior to PFS event
  - Discontinuation of study treatment prior to PFS event
  - **IE handling strategy:** Following treatment policy the IE will be ignored, and tumor assessment data collected after the IE will be included in the PFS analysis
- **Population-level summary:** HR

9.4.4 Main Analytical Approach for Primary Estimand

If participants have any IE(s), then the treatment policy as defined above to handle the IEs will be implemented. Otherwise, data for participants without the occurrence of disease progression or death as of the CCOD will be censored at the time of the last tumor assessment prior to the CCOD (or at the time of randomization plus 1 day if no tumor assessment was performed after the randomization). PFS will be compared between treatment arms using the stratified log-rank test. The HR will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors used will be the same as the randomization stratification factors (as entered in IxRS). Results from an unstratified analysis will also be provided as a sensitivity analysis. If, at the time of analysis, it is deemed that the smallest stratum per has <5 patients, unstratified analyses will be used as the primary analysis. For each treatment arm, Kaplan-Meier methodology will be used to estimate the median PFS, and the Brookmeyer-Crowley method will be used to construct the 95% CI for the median PFS. Kaplan-Meier curves will also be produced.

9.4.5 Sensitivity Analyses

In order to assess the robustness of the estimated treatment effect following sensitivity analysis will be performed:

- **PFS assessed by investigator based on unstratified analysis:** To assess the impact of stratification (as entered in the IxRS) the main analytical approach for the primary estimand described in the Section 9.4.4 will be repeated without the stratification factors.
- **PFS assessed by investigator based on interval censoring approach:** To assess the impact of missing scheduled tumor assessments, the PFS will be assessed by performing a sensitivity analysis based on the interval censoring method.
- **PFS assessed by Independent Review Committee:** A BICR audit of a prespecified subset of PFS data will be planned and detailed separately in an IRC charter. In the case of any discordance, additional sensitivity analysis for PFS may be performed by repeating PFS analysis (Section 9.4.3) with data from BICR assessment.

Further details on sensitivity analysis will be detailed in the SAP.

9.4.6 Supplementary Estimand

In order to better characterize the treatment effect, two supplementary analyses as outlined below based on different strategy of handling IE are planned for PFS.

Note that the attributes of population, variables and population-level summary will remain the same as the primary estimand (Section 9.4.3).

- **PFS assessed by investigator based on hypothetical strategy for use of any NPT prior to PFS event:** To assess the impact of NPT use prior to PFS event, the

primary analysis of investigator-assessed PFS will be repeated with the IEs handled using a hypothetical strategy. According to this strategy, participants who start a NPT prior to the PFS event will be censored at the time of the last disease status assessment before the initiation of a NPT. If participants start any NPT before starting study treatment, then the data for those participants will be censored at the time of randomization plus day 1. Approaches to handle other IEs (discontinuation of study treatment prior to PFS event) and the analysis method will be the same as the primary estimand.

- **PFS assessed by investigator based on composite strategy for use of any NPT prior to PFS event:** In addition to the above estimand, another supplementary estimand for PFS will be estimated using the following composite strategy. According to the composite strategy, use of any NPT prior to PFS event will be considered as a PFS event (progression) at the time of initiation of NPT. If participants start any NPT before starting study treatment, then the data of participants will be censored at the time of randomization plus Day 1. Approaches to handle other IE (discontinuation of study treatment prior to PFS event) and analysis method will be the same as primary estimand.

Further supplementary analyses may be performed, and details will be prespecified in the SAP.

9.4.7 Secondary Endpoints

The secondary efficacy and safety endpoints are defined in Table 6. The subset of corresponding secondary efficacy endpoints which are not derived from PRO measures, are expressed using the estimand framework. The analysis method for all the secondary endpoints are described in following subsections.

9.4.7.1 Overall Survival

The secondary comparison of interest is the HR OS. The secondary trial objective is to demonstrate superiority of the Phesgo plus giredestrant arm over the Phesgo arm.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population:** As defined for the primary estimand in Section 9.4.3
- **Variable:** OS, defined as time from randomization to death from any cause
- **Treatment:** As defined for the primary estimand in Section 9.4.3
- **IEs and handling strategy:**
  - Use of any NPT (as detailed in Section 6.8.2) prior to disease progression
  - Discontinuation of study treatment prior to disease progression
  - **IE handling strategy:** Following treatment policy the IE will be ignored, and OS observations collected after the IE will be used.
- **Population-level summary:** HR for OS.

As specified in Section 4.1.1, cross over between the two treatment arms will not be allowed and hence it is not anticipated as an IE. If participants have any IEs described above, then the strategies defined below to handle the IEs will be implemented. Otherwise, data for participants who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Data from participants without postbaseline information will be censored at the date of randomization plus 1 day.

OS will be hierarchically tested if the primary endpoint, PFS, is statistically significant at the primary PFS analysis. Refer to Section 9.5 for details on interim analysis for OS.

9.4.7.2 Objective Response Rate

The analysis population for ORR will be full analysis set i.e., all participants assigned to treatment groups as randomized by the IxRS. Participants with no measurable disease at baseline, including participants without any postbaseline tumor assessment, will be considered non-responders.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population:** As defined for the primary estimand in Section 9.4.3.
- **Variable:** ORR (following induction therapy), 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
- **Treatment:** As defined for the primary estimand in Section 9.4.3
- **IEs and handling strategy:**
  - As defined for the primary estimand in section 9.4.3.
  - IE Handling Strategy: Following treatment policy, all the IEs will be ignored, and tumor assessment data collected after the IE will be included in the ORR analysis
- **Population-level summary:** Difference in proportion.

An estimate of ORR and 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. Odds ratio will be calculated and ORR will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors to be used will be the same as those used for the analysis of the primary endpoint. The difference in ORR between treatment arms will be calculated, and 95% CI will be calculated using the Newcombe methodology (Newcombe 1998).

9.4.7.3 Clinical Benefit Rate

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population:** As defined for the primary estimand in Section 9.4.3.
- **Variable:** CBR (following induction therapy), 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
- **Treatment:** As defined for the primary estimand in Section 9.4.3
- **IEs and handling strategy:**
  - As defined for the primary estimand in Section 9.4.3
  - **IE handling Strategy:** Following treatment policy, all the IEs will be ignored, and tumor assessment data collected after the IE will be included in the ORR analysis
- **Population-level summary:** Difference in proportion

CBR analysis including handling of IE will follow the same methods as those used for ORR

9.4.7.4 Duration of Response

Analysis of duration of response (DOR) will include only participants who had an objective response. Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population:** All randomized participants who had an OR
- **Variable:** DOR (following induction therapy), defined as the time from the first occurrence of a documented OR to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- **Treatment:** As defined for the primary estimand in Section 9.4.3
- **IE and handling strategy**
  - As described for the primary estimand in Section 9.4.3
  - IE handling Strategy: Following treatment policy, all the IEs will be ignored, and tumor assessment data collected after the IE will be included in the DOR analysis
- **Population-level summary:** HR

Handling of IEs will follow the same methods as those used for PFS. Data for participants who have not progressed and who have not died at the time of analysis will be censored at date of the last tumor assessment. The Kaplan-Meier approach will be used to estimate the median DOR and to construct survival curves for each treatment arm for a visual description of the difference among arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median (Brookmeyer and Crowley 1982).

9.4.7.5 *Patient*-Reported Outcome

The secondary efficacy objective of the study is based on the following PRO endpoints:

- Mean and mean changes from baseline score in function (role, physical) and HRQoL by cycle and between treatment arms as assessed by the functional and GHS/QoL scales of the EORTC QLQ-C30

The full analysis set will be used to document PRO completion rates.

Summary statistics (mean, standard deviation, median, and range) of absolute scores and mean changes from baseline will be calculated for the functional (role [Question {Q}6, Q7], physical [Q1–Q5]) and the GHS/QoL (Q29, Q30) scales of the EORTC QLQ-C30 at each assessment timepoint for each arm. The mean (and 95% CI) and median of the absolute scores and the changes from baseline will be reported for interval and continuous variables. Previously published minimally important differences will be used to identify meaningful change from baseline within each treatment group on the functional and GHS/QoL scales (Osoba et al. 1998; Cocks et al. 2011).

The EORTC QLQ-C30 (Version 3) data will be scored according to the EORTC scoring manual (Fayers et al. 2001). PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm. Details of the analyses, including methods for handling missing data, will be specified in the SAP.

9.4.7.6 Safety

As defined in Section 9.3, there will be two safety populations to summarize safety events by different phase (induction therapy phase, maintenance phase or both combined) of the study.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and primary and secondary cardiac endpoints.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

Cardiac-specific adverse events will focus on the incidence of participants with heart failure (NYHA, NCI CTCAE [heart failure] Grades 2, 3, 4, and 5). LVEF data summaries will include the incidence of participants with LVEF decreases with an absolute decrease of at least 10 percentage points from baseline and to below 50%.

Safety analyses will be performed at the primary analysis and may be performed at additional time point during the study as necessary.

9.4.8 Exploratory Endpoints

The exploratory objective for this study is to evaluate the efficacy of Phesgo plus giredestrant compared with Phesgo from the participant's perspective based on the following endpoints:

- Mean and mean changes from baseline score in disease/treatment-related symptoms by cycle and between treatment arms as assessed by all symptom items/scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
- Proportion of participants reporting a clinically meaningful deterioration in pain severity, defined as a $\geq$2-point increase from baseline on the “worst pain” item score from the BPI-SF questionnaire
- Changes in patient-reported WPAI scores at specified timepoints
- To evaluate health utility of participants treated with Phesgo plus giredestrant compared with Phesgo to generate utility scores for use in economic models

The analysis of above exploratory efficacy endpoints will be described in the SAP.

9.4.9 Other Safety Analyses

The exploratory safety objective for this study is to evaluate safety of Phesgo plus giredestrant compared with Phesgo from the participant's perspective based on the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities (nausea, vomiting, diarrhea, rash, joint pain, fatigue, hot flashes) (see Appendix 5), as assessed through use of the NCI PRO-CTCAE.
- Proportion of participants reporting each response option at each assessment timepoint by treatment arm for treatment side-effect bother single-item GP5 from the FACT-G

- Change from baseline in symptomatic treatment toxicities and treatment side-effect bother, as assessed through use of the PRO-CTCAE and the overall treatment side-effect bother item, respectively.

The population to be used for the analysis of PRO-CTCAE is the safety evaluable population. PRO-CTCAE analyses will be descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities over the course of the study. The numeric scores indicate an ordinal, rather than continuous outcome; therefore, analysis will focus on frequency counts and percentages. The number and percentage of participants reporting each symptom and the change from baseline by category (frequency of occurrence, severity, or interference) will be summarized at each assessment time point by treatment arm. The worst postbaseline score will be summarized per treatment group, for each individual attribute and adverse event, and shift tables will be provided per treatment group. For items rated on a 5-point Likert scale, the maximum postbaseline score and change from baseline will be summarized by treatment arm.

Results from these exploratory analyses will be presented separately from the safety analyses. PRO-CTCAE data will be analyzed at the item level. Graphical representation of PRO-CTCAE data over time will also be provided and summarized over time. These analyses will also apply to the GP5 overall treatment side-effect bother item. A descriptive analysis of absolute scores and the proportion of participants selecting each response option at each assessment time point by treatment arm will be reported for the FACT-G single-item GP5 as well as graphical representation of PRO-CTCAE data over time will also be provided and summarized over time. The proportion of missing data at each assessment time point will also be summarized to facilitate interpretation of data.

9.4.10 Other Analyses

9.4.10.1 Summaries of Conduct of Study

Randomization, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations regarding the inclusion and exclusion criteria, will be summarized by treatment arm.

9.4.10.2 Summaries of Treatment Group Comparability

The evaluation of treatment group comparability between the treatment arms will include summaries of demographic and baseline characteristics, including stratification factors and participant treatment history. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for ca*tegorical* variables.

9.4.10.3 Biomarker Analysis

The exploratory biomarker objective are detailed in Table 6. No formal statistical analysis of exploratory biomarkers will be performed. Analysis of relationship of biomarkers with efficacy endpoints (e.g., PFS and OS) as well as with safety, PK,

immunogenicity and other biomarkers, as appropriate will be explored. Results of this exploratory analysis may be presented in a separate report.

9.4.10.4 Pharmacokinetic Analyses

Giredestrant plasma concentration data will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, standard deviations, coefficient of variation (%CV), and others as appropriate.

The pertuzumab and trastuzumab concentrations (within Phesgo) in serum will also be tabulated and summarized. Descriptive statistics will include means, medians, ranges, standard deviations, coefficient of variation (%CV), and others as appropriate.

Additional PK (e.g. population PK) and ER analyses may be conducted as appropriate.

9.4.10.5 Immunogenicity Analyses

The immunogenicity analysis population will consist of all *participants in A*rm B in the maintenance phase who have at least one anti-drug antibody (ADA) assessment. Subjects will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, participants are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Participants are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status efficacy, safety and PK endpoints will be analyzed and reported via descriptive statistics.

9.5 INTERIM ANALYSIS

9.5.1 Planned Interim Analysis

No interim analyses of the primary endpoint (PFS) will be performed.

However, the study will incorporate three OS analyses (two interim analyses and one final analysis). OS will be hierarchically tested if the primary endpoint, PFS, is statistically significant. The first OS interim analysis will be at PFS primary analysis with projected ~163 deaths, second OS interim analysis with projected ~298 deaths at ~84

months after the first participant is randomized and final OS analysis with projected ~387 deaths (80% power) at ~122 months after the first participant is randomized. The Lan-DeMets implementation of the O'Brien and Fleming alpha-spending function will be used to control the overall type I error for the OS comparison at a two-sided 0.05 significance level. Table 9 summarizes the assumptions and characteristics of the interim and final analyses for OS.

Table 9 Assumptions and Characteristics for the Interim and Final Analyses of Overall Survival

Assumption	Findings
HR targeted	0.75
Median OS for control arm (Phesgo)	60 months
Median OS for treatment arm (Phesgo plus giredestrant)	80 months
Projected enrollment period (same as PFS)	36 months
First interim analysis of OS (to be performed at time of Primary PFS analysis)	
Estimated cutoff date [a]	50 months
Projected number of events (% of final events)	163 (42.1%)
Projected Efficacy boundary (p-value)	0.599 (<0.001)
Second interim analysis of OS	
Estimated cutoff date [a]	84 months
Projected number of events (% of final events)	298 (77.0%)
Projected Efficacy boundary (p-value)	0.765 (<0.0210)
Final analysis of OS	
Estimated cutoff date [a]	122 months
Projected number of events (% of final events)	387 (100%)
Projected Efficacy boundary (p-value)	0.815 (<0.0436)
Power	80%
Overall αlevel (two-sided) 0.05	0.05

HR =hazard ratio; OS =overall survival; PFS=progression-free survival;
OS =overall survival.

[a] Estimated data cutoff time from first randomization. Analysis results will be made available after data cleaning.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, *Clinical Trials Directive (2001/20/EC) or Clinical Trials* Regulation 536/2014 (E*EA* sites only), and all other applicable local regulations.

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant’s legally authorized representative.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data and data on genomic variants may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and*/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–6 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study

initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–7 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–8 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 300 sites globally will participate to randomize approximately 730 participants. Randomization will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker, and pharmacokinetic analyses), as specified in Section 8. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate participant safety throughout the study. An IRC will collect, store, and potentially review imaging data.

A Steering Committee will be set up to provide guidance on the protocol and study design and to provide guidance on review of any relevant study-related documents or procedures.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as

specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

A2–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a participant or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

    Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A2–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A2–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A2–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A2–5 for reporting instructions).

A2–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A2–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the electronic Case Report Form (eCRF).

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A2–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table A2-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A2-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A2–5 for reporting instructions), per the definition of serious adverse event in Section A2–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A2–5 for reporting instructions), if they meet the definition of serious adverse events and as per the definition of serious adverse event in Section A2–2.

A2–3.2.1 Assessment of Severity for LVSD (Heart Failure)

Symptomatic LVSD (also referred to as congestive heart failure [CHF]) will be assessed as “heart failure” on the basis of NCI CTCAE v5.0 (see Table A2-2) and NYHA classification (Table A2-3).

Table A2-2 LVSD National Cancer Institute Common Terminology Criteria for Adverse Events Version 5 Grading

Investigations					
	Grade				
	1	2	3	4	5
Ejection fraction decreased [a]	—	Resting EF 50% – 40%; 10% – 19% drop from baseline	Resting EF 39% – 20%; > 20% drop from baseline	Resting EF < 20%	—
Cardiac Disorders					
	Grade				
	1	2	3	4	5
Heart failure [b]	Asymptomatic with laboratory (e.g., BNP [B-natriuretic peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death

BNP = B-natriuretic peptide; EF = ejection fraction; LVSD = left ventricular systolic dysfunction.

[a] Definition: the percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.

[b] Definition: a disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or the ability to do only at an elevation in the filing pressure.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Table A2-3 NYHA Functional Classification System for Heart Failure

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

A2–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

For participants receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A2–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A2–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the

Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health-care professionals.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A2–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A2–4 REPORTING OF SERIOUS ADVERSE EVENTS

A2–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A2–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2–5.

A2–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2–5.

A2–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A2–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A2–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event /Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing

the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 28 days after the final dose of study treatment are provided in Section A2–5.

A2–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 days after the final dose of study treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF. Heart failure, irrespective of causal relationship, should also continue to be reported during the 3 years after Phesgo discontinuation.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event /Special Situations Form, using the fax number or email address provided to investigators.

A2–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A2–7.1 ADMINISTRATION-RELATED REACTIONS: INJECTION-RELATED REACTIONS AND INJECTION SITE REACTIONS

Adverse events considered to be injection reactions (see Appendix A3-3.1.1) that occur during or within 24 hours after Phesgo administration and are judged to be related to Phesgo should be captured as a diagnosis (e.g., “injection-related reaction”, “injection site reaction”, or "anaphylactic reaction” on the Adverse Event eCRF). If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

A2–7.2 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A2–7.3 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF

- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A2–7.4 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A2–4 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A2–7.5 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A2–7.4 for details on recording persistent adverse events).

A2–7.6 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A2–7.4 for details on recording persistent adverse events).

A2–7.7 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) 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). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A2–7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A2–5).

A2–7.8 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1) that are attributed by the investigator solely to progression of breast cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A2–5). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section A2–6.

A2–7.9 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A2–7.10 LACK OF EFFICACY OR WORSENING OF BREAST CANCER

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A2–7.11 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A2–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or insertion of access device for study treatment administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition

  - The participant has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A2–7.12 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

  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 and adverse events associated with special situations are to be reported separately on the Adverse Event eCRF, as outlined in the sections below.

A2–7.12.1 Reporting Special Situations

All special situations associated with Phesgo or giredestrant, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the name of the drug and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the name of the drug and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected,

check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box}

- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the name of the drug and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the name of the drug and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the name of the drug and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the name of the drug and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the name of the drug and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the name of the drug and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the name of the drug and "participant supplied drug to third party" as the event term. Check the "Drug misuse" box.

A2–7.12.2 Reporting Adverse Events Associated with Special Situations

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills 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; see Section A2–5). For Phesgo or giredestrant, adverse events associated with special situations should be recorded as described below for each situation boxes.

- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

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 (special situation) and one entry to report the headache (adverse event). The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

A2–7.13 *PATIENT-REPORTED* OUTCOME DATA

Adverse event reports will not be derived from PRO-CTCAE or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile participant reports of treatment-related symptoms (via PRO-CTCAE) with investigator reports of adverse events. Sites are not expected to review the PRO-CTCAE or other PRO data for adverse events.

A2–7.14 ASYMPTOMATIC LVEF DECLINES AND SYMPTOMATIC LVSD (HEART FAILURE)

Asymptomatic declines in LVEF should not be reported as adverse events because LVEF data are collected separately in the eCRF (Table A2-4). Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF of ≥ 10 percentage points from baseline to an LVEF $< 50\%$ must be reported as an adverse event with the term of “ejection fraction decreased”, as per NCI CTCAE v5.0 (Table A2-2). In addition, a comment in the adverse events comments field should confirm that the event was asymptomatic.
- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment is an adverse event of special interest and must be reported in an expedited manner (see Section 8.3.8.1). The event must be reported as an adverse event with the term of “ejection fraction decreased”, as per NCI CTCAE v5.0 (Table A2-2) and a comment should be added to the adverse events comments field confirming that the event was asymptomatic.

Symptomatic LVSD (referred to as heart failure) should be reported as a serious adverse event according to the conventions in Table A2-4). If the diagnosis is heart failure, it should be reported as such, and not as individual signs and symptoms of heart failure. Signs and symptoms should be recorded in the Additional Details section of the Serious Adverse Event eCRF. Heart failure should be graded according to both NCI CTCAE v5.0 (Table A2-2) and NYHA Class (Table A2-3). LVEF results must also be reported.

Guidelines for management of participants who develop left ventricular dysfunction are provided in Appendix A3–3.1.2.

Table A2-4 Reporting Conventions for Left Ventricular Systolic Dysfunction/Congestive Heart Failure

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decline in LVEF of < 10 percentage points from baseline or to an LVEF of ≥ 50%	No additional reporting required; LVEF results to be reported in the eCRF	NA	NA
Asymptomatic decline in LVEF of ≥ 10 percentage points from baseline [a] to an LVEF of < 50%	AE [b] (AE eForm)	Ejection fraction decreased [a]	NCI CTCAE for “ejection fraction decreased”
Asymptomatic decline in LVEF requiring treatment or leading to study treatment discontinuation	AE (AE eForm) and report as a non-serious AEs of special interest on an SAE eForm	Ejection fraction decreased [a]	NCI CTCAE for “ejection fraction decreased”
Heart failure / CHF (symptomatic LVSD)[c]	AE (AE eForm) and SAE (SAE eForm)	“Heart failure ”	NCI CTCAE for "heart failure" and NYHA class

AE = adverse event; CHF = congestive heart failure; eForm = electronic form; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; NA = not applicable; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association; SAE = serious adverse event.

[a] Baseline is considered the last LVEF prior to enrolling in study.

[b] Report the status as asymptomatic and provide the LVEF value in the comments field as appropriate.

[c] Any symptomatic LVSD event must be reported as “heart failure.”

Appendix 3
Safety Plan: Management of Identified and Potential Risks

A3–1 RISKS ASSOCIATED WITH PHESGO

The pertuzumab and trastuzumab drug substances in Phesgo are identical to the drug substances in the Perjeta, Herceptin IV, and Herceptin SC formulations. The safety plan for participants in this study is based on the anticipated safety risks of Phesgo as observed in Phase III Study WO40324 and Phase II Study MO40628 and on clinical experience with Perjeta IV and with Herceptin IV and SC, in completed and ongoing studies. The anticipated important safety risks for Phesgo are outlined below. Please refer to the Phesgo, and the Perjeta and Herceptin Investigator's Brochures for a complete summary of safety information.

Several measures will be taken to ensure the safety of participants participating in this study. Eligibility criteria have been designed to exclude participants at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for discontinuation, are provided below.

A3–1.1 HYPERSENSITIVITY REACTIONS/ANAPHYLAXIS AND ADMINISTRATION-RELATED REACTIONS

In Phase III Study WO40324, administration-related reactions (ARRs) occurring within 24 hours of HER2-targeted therapy were slightly higher in the Phesgo arm compared to the PH intravenous (IV) arm (34 [13.5%] PH IV vs. 43 [17.3%] Phesgo participants). The most frequently reported preferred terms (in $\geq$ 5% of cases) included injection site reaction: 1 (0.4%) PH IV (occurred in a participant who switched to Herceptin SC during the adjuvant treatment period) versus 32 (12.9%) Phesgo participants; and infusion-related reaction: 25 (9.9%) PH IV versus 0 (0%) Phesgo participants. The injection site reactions, related to the SC route of administration of Phesgo, are the main reason for the observed numerical imbalance of ARRs.

The majority of ARRs were Grade 1 and 2, with Grade 1 events more frequent in the Phesgo arm (18 [7.1%] PH IV vs. 38 [15.3%] Phesgo participants). Three participants in the PH IV arm and none in the Phesgo SC arm experienced Grade 3 events.

The majority of ARR events occurred during the neoadjuvant phase of the study. The ARRs led to withdrawal from the study for two participants (one in each arm).

Overall, hypersensitivity and anaphylaxis events occurred with low and comparable incidence across the treatment arms (5 [2.0%] PH IV vs. 4 [1.6%] Phesgo participants). Except for one event (Grade 3 hypersensitivity related to a concomitant medication at study Cycle 4 in the PH IV arm), all events occurred after study Cycle 5 (first administration of HER2-targeted therapy) and were related to HER2-targeted therapy

(4 [1.6%] participants in each arm). The reported events by PT were injection-related reaction, hypersensitivity, and drug hypersensitivity. All events were Grade 1 (three participants per arm) or Grade 2 (one participant per arm).

The majority of anaphylaxis and hypersensitivity events occurred during the neoadjuvant phase of the study. The incidence of anaphylaxis and hypersensitivity adverse events related to HER2 reported during or within 24 hours of administration were low in both arms (2 [0.8%] PH IV vs. 2 [0.8%] Phesgo), and all low grade (Grade 1 and Grade 2). Three of the events occurred during the first administration of HER2-targeted therapy (study Cycle 5), and one event occurred during the sixth administration of HER2-targeted therapy (study Cycle 10). Of these, two events (one in each arm) occurred during/immediately after HER2-targeted therapy, both during the first administration of HER2-targeted therapy study Cycle 5. Each of these events led to withdrawal from HER2-targeted therapy. Participants should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in participants treated with Phesgo, caution should be exercised as these have been associated with IV pertuzumab in combination with trastuzumab and chemotherapy.

Guidelines for management of participants who develop hypersensitivity/anaphylaxis and ARR are located in Section A3–3.1.1. Refer to the Phesgo and the Perjeta and Herceptin Investigators' Brochures for the most recent data related to the risk of hypersensitivity reactions.

A3–1.2 SYMPTOMATIC LEFT VENTRICULAR DYSFUNCTION

In Phase III Study WO40324, primary cardiac events were defined as either:

- Symptomatic ejection fraction decrease (Heart Failure) NYHA Class III or IV and a drop in LVEF of at least 10 percentage points from baseline and to below 50%.
- Cardiac death, defined as one of the following:
  - Definite cardiac death, defined as death due to heart failure, myocardial infarction, or documented primary arrhythmia
  - Probable cardiac death, defined as sudden unexpected death within 24 hours of a definite or probable cardiac event (e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia) without documented etiology

There were no participants in the PH IV arm and 2 (0.8%) participants in the Phesgo arm who met the criteria for a primary cardiac event: 1 (0.4%) participant had heart failure with LVEF drop of at least 10 percentage points from baseline and to below 50%, and 1 (0.4%) participant with cardiac death.

The event of heart failure was reported in an elderly participant in the Phesgo arm. The onset of the adverse event occurred 18 days after Cycle 4 Day 1 of doxorubicin (Adriamycin®) plus cyclophosphamide (AC) every 3 weeks, and became serious 12 days after Cycle 6 Day 1 of Phesgo. The overall diagnosis was an event of heart failure (NYHA Class IV) assessed by the investigator as related to HER2 treatment. It led to withdrawal of Phesgo treatment and had resolved at the time of the CCOD.

The event of cardiac death was reported in an elderly participant in the Phesgo arm. The event was due to an acute myocardial infarction which occurred after Cycle 2 of dose-dense doxorubicin plus cyclophosphamide (ddAC) (i.e., prior to the start of HER2-targeted therapy).

Both primary cardiac events occurred during the neoadjuvant phase of the study. No primary cardiac events were reported in participants in the adjuvant or treatment-free follow-up period.

Secondary cardiac events were only counted for participants who had not experienced a primary cardiac event (i.e., participants could only be counted in one of these categories). Those events not counted as a secondary cardiac event were still captured as part of adverse event reporting (ejection fraction decreased) and under LVEF assessment.

Overall, 9 (3.6%) versus 4 (1.6%) participants had at least one LVEF decrease of 10 % below the baseline measurement to an absolute LVEF value of $<50\%$ in the PH IV and Phesgo arms, respectively. Of these, the initial LVEF decline was confirmed by a second LVEF assessment for 2 (0.8%) participants in the PH IV arm and 1 (0.4%) participant in the Phesgo arm; therefore overall, 3 participants fulfilled the criteria for secondary cardiac events.

Secondary cardiac events occurred throughout all phases of the study. Some participants, are counted in multiple outputs if they had events occurring in more than one phase of the study. The number of participants who experienced at least one LVEF decrease of 10% below the baseline measurement to an absolute LVEF value of $<50\%$ during study were:

- Four (1.6%) and one (0.4%) events in the PH IV and Phesgo arms, respectively, which occurred during the neoadjuvant phase Four (1.6%) and three (1.2%) events in the PH IV arm and Phesgo arms, respectively, which occurred during the adjuvant phase
- Three (1.2%) and one (0.4%) events in the PH IV arm and Phesgo arms, respectively, which occurred during the follow-up phase

Participants with significant cardiac disease or baseline LVEF < 50% are not eligible for this study. Similar to all Perjeta trials, participants must undergo routine cardiac monitoring by ECHO or MUGA scans as described in Section 8.2.4.1 and the schedule of activities (see Section 1.3).

During the screening/baseline period, complete medical history information will be collected from all participants to explore possible risk factors for treatment-associated congestive heart failure (CHF). If symptomatic LVSD (heart failure; serious adverse event of NCI CTCAE v5.0 Grade 3 or 4; NYHA Class III or IV; see Appendix A3–3.1.2) develops, the participant must be monitored carefully with repeat LVEF assessments. Symptomatic LVSD should be treated and followed according to standard medical practice. Refer to the Phesgo, and the Perjeta and Herceptin Investigator's Brochures for the most recent data relating to risk of LVSD and CHF.

Guidelines for management of participants who develop left ventricular dysfunction are provided in Appendix A3–3.1.2.

A3–1.3 DIARRHEA

In Phase III Study WO40324, the incidence and severity of diarrhea events were comparable between the two treatment arms (55.2% PH IV participants vs. 58.5% Phesgo participants). The majority of diarrhea events were Grade 1 and 2 in both arms. The incidence of Grade 3 diarrhea was low and balanced between the two treatment arms (11 [4.4%] PH IV vs. 17 [6.9%] Phesgo participants). There was one Grade 4 event in the PH IV arm which was assessed as related to paclitaxel by the investigator. No Grade 5 (fatal) events occurred in either arm.

Incidence of all grade diarrhea related to HER2 was comparable between the two treatment arms (32.5% PH IV vs. 30.6% Phesgo participants). Grade 3–4 diarrhea events related to HER2 were reported in 5 (2.0%) PH IV versus 9 (3.6%) Phesgo participants. No events of diarrhea led to withdrawal of HER2-targeted therapy.

Guidelines for management of participants who develop diarrhea are provided in Appendix A3–3.1.3.

A3–1.4 RASH/SKIN REACTIONS

In the Phase III Study WO40324, there was only one event of serious rash/skin reaction in the Phesgo arm, classified as Grade 2 (erythema event).

The rash/skin reaction appeared to be treatable in some participants with standard acne therapies, including topical and oral antibiotics.

Guidelines for management of participants who develop rash/skin reaction are provided in Appendix A3–3.1.3.

A3–1.5 MUCOSITIS

In the Phase III Study WO40324, the incidence of serious mucositis events were low in both treatment arms (4/252 participants [1.6%] in PH IV arm vs. 3/248 participants [1.2%] in the Phesgo arm), with the majority of them (in 6 participants overall) being Grade 3 in severity.

Guidelines for management of participants who develop mucositis are provided in Appendix A3–3.1.3.

A3–1.6 REPRODUCTIVE RISKS ASSOCIATED WITH PERTUZUMAB, TRASTUZUMAB, AND PHESGO

Reproductive toxicity was identified during nonclinical studies with Perjeta. Perjeta administered to pregnant cynomolgus monkeys during organogenesis led to delayed renal development, oligohydramnios, and embryofetal deaths. However, reproductive toxicity studies with trastuzumab conducted in female cynomolgus monkeys revealed no trastuzumab-related embryotoxicity or effects on fetal development. There are no clinical studies of trastuzumab or pertuzumab in pregnant women. The IgGs are known to cross the placental barrier. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herceptin. Therefore, neither pertuzumab nor trastuzumab should be used during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

Contraception guidelines are in Section 5.1 and pregnancy monitoring is in Appendix 4.

A3–1.7 INTERSTITIAL LUNG DISEASE

In the Phase III Study WO40324, incidence of interstitial lung disease (ILD) adverse events was low and balanced between the two treatment arms (2 [0.8%] PH IV vs. 3 [1.2%] Phesgo participants). Both events in the PH IV arm occurred prior to HER2-targeted therapy and were assessed as related to chemotherapy.

In the Phesgo arm, serious adverse events were reported in 1 (0.4%) and 2 (0.8%) participants with ILD which were assessed by the investigator as related to AC chemotherapy and HER2- targeted therapy, respectively. All events were Grade 2, and had resolved by the time of CCOD.

A3–1.8 FEBRILE NEUTROPENIA/NEUTROPENIA

In the Phase III Study WO40324, the incidence and severity of neutropenia/febrile neutropenia/leukopenia adverse events were comparable between the two treatment

arms (133/252 patients [52.8%] in P+H IV arm vs. 119/248 patients [48.0%] in PH FDC SC arm). The majority of these events were Grade 3-4 in severity, with a low incidence of febrile neutropenia (5.6% vs. 6.5%, respectively).

Guidelines for management of participants who develop febrile neutropenia/neutropenia are provided in Appendix A3–3.1.4.

A3–2 RISKS ASSOCIATED WITH GIREDESTRANT

Giredestrant is not approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with giredestrant in completed and ongoing studies. On the basis of clinical data available to date, the following identified (known) and potential (anticipated) risks for giredestrant are outlined below. Please refer to the giredestrant Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants. Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. An iDMC will review safety data regularly throughout the study (see Appendix 1). In addition, guidelines for managing adverse events (see Table A3-1), including criteria for treatment interruption or discontinuation, are provided below.

A3–2.1 IDENTIFIED RISKS ASSOCIATED WITH GIREDESTRANT

A3–2.1.1 Gastrointestinal Toxicities

Gastrointestinal (GI) effects, such as diarrhea and nausea, were very common (≥ 10%) in participants treated with giredestrant, and vomiting was seen with common (≥ 1– < 10%) frequency. These were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. Participants receiving treatment with giredestrant should be closely monitored for GI effects and any consequent sequelae, such as changes in blood chemistry parameters or dehydration. Supportive care should be followed per institutional guidelines.

A3–2.1.2 Arthralgia

Arthralgia was very common (≥ 10%) in participants treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. Management of arthralgia should be according to local standard of care and institutional guidelines.

A3–2.1.3 Musculoskeletal Pain

Musculoskeletal pain was very common (≥10%) in participants treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity.

Management of musculoskeletal pain should be according to institutional guidelines.

A3–2.1.4 Hot Flush

Hot flush was common (≥1–<10%) in participants treated with giredestrant in line with giredestrant's anti-estrogenic pharmacologic activity. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. Hot flush should be managed according to institutional guidelines.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) have both been shown to be safe and to reduce the severity of hot flushes in participants with BC, although special caution should be exercised when using these agents in conjunction with tamoxifen. In participants using tamoxifen, SNRIs should be used over SSRIs due to less potent inhibition of the cytochrome P450 2D6 isozyme pathway required for tamoxifen metabolism, which could lead to reduced efficacy of tamoxifen. Other pharmacological options for the treatment of hot flushes may include gabapentin, clonidine, or alternative herbal agents (Franzoi et al. 2021).

A3–2.1.5 Dizziness

Dizziness was very common (≥10%) in participants treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. Dizziness should be managed according to institutional guidelines.

A3–2.1.6 Fatigue

Fatigue was very common (≥ 10%) in participants treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. Fatigue should be managed according to institutional guidelines.

A3–2.1.7 Hepatoxicity

Events of aspartate aminotransferase increased and/or alanine aminotransferase increased, were very commonly reported in patients treated with giredestrant (≥10%). Events of blood bilirubin increased were commonly reported (≥1 to <10%). 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, with treatment, or without any intervention.

However, from across the entire development program (n=1260), there were a total of three serious cases. All three serious cases were assessed as related to giredestrant by

the reporting investigator. Please refer to Giredestrant Investigator Brochure v6 for more information. Recommended management guidelines are provided in Table A3-1.

A3–2.1.8 Bradycardia

Dose-dependent decreases in heart rate have been observed with treatment with giredestrant. Bradycardia is an identified risk with giredestrant that has been observed with common frequency (≥1 to <10%). All cases of bradycardia were non serious and mild to moderate, with cases being asymptomatic/Grade 1 in maximum severity. The vast majority of cases resolved without intervention or interruption of study drug.

No clinically significant ECG changes, exercise intolerance, or changes in systolic or diastolic blood pressure were reported because of heart rate decrease. Follow-up data from participants treated with giredestrant showed complete reversibility upon discontinuation of giredestrant treatment.

ECGs will be collected for routine safety monitoring during this study (see 8.2.4.2). Investigators should use medical judgment and exercise caution when considering the co-administration of drugs known to cause decrease in heart rate and/or bradycardia and consider using alternative treatment if possible (see Sections 6.8.2 and 6.8.4). In participants with preexisting baseline conditions for which they are already receiving a stable dose of β-blockers or calcium-channel antagonists, investigators should carefully monitor participants for worsening of bradycardia following study treatment and follow the recommended management guidelines as noted in Table A3-1.

A3–2.1.9 Headache

Headache was commonly reported in patients treated with giredestrant (≥1 to <10%). Cases were non-serious and Grade 1 or Grade 2 in severity. Most headache events resolved without treatment.

A3–2.2 Potential Risks Associated with Giredestrant

Information described below on potential risks is based on data from the Phase I GO39932 clinical study as of CCOD *17 September* 2021.

A3–2.2.1 Venous Thromboembolic Events (Including Pulmonary Embolism)

Thromboembolic events occur in participants with malignancies, and the risk may be increased by suppression of estrogen receptor signaling. *In Study GO39932, one serious Grade 3 event of pulmonary embolism occurring in a patient receiving giredestrant at the higher dose of 100 mg and a non-serious case of Grade 2 deep vein thrombosis occurring in a patient receiving 100 mg giredestrant dose in combination with palbociclib treatment. Both cases were assessed as unrelated to giredestrant.*

Please refer to the current version of the Giredestrant Investigator's Brochure for more information. Participants should be closely monitored for signs and symptoms of thrombosis and instructed to immediately seek medical attention if thrombosis is suspected.

A3–2.2.2 Renal Toxicity or Increased Creatinine

Dose-dependent effects on the kidneys were observed in repeat-dose studies in both rats and monkeys given giredestrant.

In Study GO39932, adverse events that might be suggestive of renal toxicity have been reported. All adverse events were non-serious and Grade 1 in maximum severity, with the exception of 3 patients who experienced Grade 2 adverse events (occurring in the 100 mg giredestrant dose cohort or in the 100 mg giredestrant +palbociclib combination cohort). Please refer to the current version of the Giredestrant Investigator's Brochure for more information. There have been no Grade 2 events in patients receiving 30 mg giredestrant single agent. No cases of acute kidney injury have been reported with single-agent giredestrant.

A3–2.2.3 Changes in Female Reproductive Organs and Menopausal Symptoms

Based on the anti-estrogenic pharmacologic activity of giredestrant, the following effects are anticipated to occur: loss of muscle and bone, vaginal dryness or discharge, irritation, mood swings, and decreased libido. These symptoms could potentially be more severe than those experienced by typical menopausal participants.

In Study GO39932, the following adverse events were reported with common frequency in patients receiving giredestrant 30 mg single agent: vulvovaginal dryness, vaginal discharge, dyspareunia, vulvovaginal pruritus, and atrophic vulvovaginitis. These events were non-serious and Grade 1 in maximum severity. Overall, across the study there was only one non-serious Grade 2 adverse events of vulvovaginal dryness occurring in a patient receiving 100 mg giredestrant dose in combination with palbociclib. No patient required any changes to dosing because of adverse events and the majority of patients did not receive treatment for the adverse events.

For management of vaginal dryness, non-hormonal vaginal lubricants and moisturizers are encouraged on a first instance (ACOG 2012).

A3–2.2.4 Female and Male Fertility

The effects of giredestrant on fertility in humans have not been studied.

In nonclinical studies, perturbation and the irreversible arrest of the estrus cycle was observed microscopically in early development *in both rats and monkeys. There was*

evidence of a return to estrus cycling following a 16-week recovery period. In nonclinical studies no microscopic effects on male reproductive organs were attributed to administration of giredestrant in a 13-week study in male rats. As th*ese* finding remain incompletely explained*,* any participants with concerns for future fertility should be made aware of this potential issue prior to joining this study. Their concerns, including fertility preservation, should be discussed prior to enrolling in any study with giredestrant.

A3–2.2.5 Embryofetal Toxicity

On the basis of the anti-estrogenic pharmacological activity of giredestrant, administration of giredestrant during pregnancy is expected to have an adverse effect and poses a risk to the human fetus, including birth defects and miscarriage.

A3–2.3 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS: PHESGO

No dose reductions are permitted for Phesgo. Further details on management of adverse events associated with Phesgo are given in the sections below.

A3–3 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

Supportive care and medical management of adverse events are at the discretion of the investigator and as per local policy, unless specifically listed below.

A3–3.1 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS: PHESGO

No dose reductions are permitted for Phesgo. Further details on management of adverse events associated with Phesgo are given in the sections below.

A3–3.1.1 Management of Hypersensitivity/Anaphylaxis and Administration-Related Reactions (Injection Reactions)

Participants should be observed closely for hypersensitivity reactions (see Section A3–1.1). Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in participants treated with Phesgo, caution should be exercised as these have been associated with Perjeta IV in combination with Herceptin IV and chemotherapy.

Hypersensitivity reactions/anaphylaxis is a systemic reaction, mediated by interactions between factors released from IgE and mast cells, resulting in an antigen-antibody reaction. Hypersensitivity reactions/anaphylaxis adverse events are likely to start mildly and increase in number and severity over time.

For Phesgo administration, participants should be monitored for at least 30 minutes after their first dose and for 15 minutes following the administration of the maintenance dose. If ARRs occur, participants must be monitored until complete resolution of signs and symptoms.

Study drug administration should be stopped in participants who develop dyspnea or clinically significant hypotension (defined per investigator's discretion).

Participants who experience any of the following events will be discontinued from study treatment (see Section 7.1)

- Grade 4 allergic reaction
- Grade 3 or 4 hypersensitivity reaction
- Acute Respiratory Distress Syndrome (ARDS)
- Bronchospasm

ARRs include:

- Injection-Related Reaction. A systemic reaction with symptoms such as chills, diarrhea, fatigue, headache, nausea, and pyrexia

  Such reactions are likely to be due to a release of cytokine(s) and typically occur during, or very shortly after, the administration of monoclonal antibodies, but they may also show a delayed onset. The majority of adverse events resolve fully.
- Injection-Site Reaction. A local reaction to the site of the injection, with signs and symptoms such as erythema, induration, swelling, pain, hypoesthesia and discomfort

Participants who experience ARRs may be managed by:

- Stopping or slowing the injection of Phesgo
- Supportive care with antihistamines, antipyretics, corticosteroids or epinephrine as clinically indicated

Participants should be monitored until complete resolution of signs and symptoms of any systemic reactions.

In order to be able to calculate time to onset of such reactions, the occurrence of associated adverse events must be documented with the date and time of the onset and duration of the event (i.e., resolution of the event).

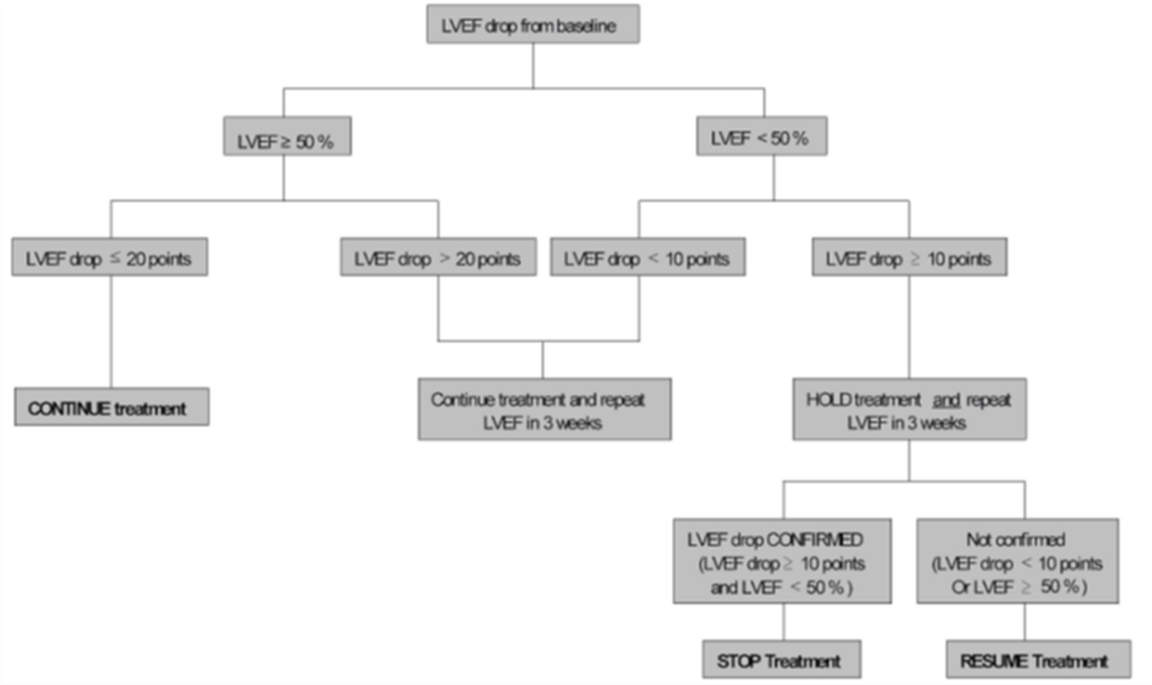
All ARRs should be recorded as described in Appendix A2–7.1.

A3–3.1.2 Management of Asymptomatic LVEF Declines and Symptomatic LVSD (Heart Failure)

All participants must have a baseline LVEF ≥ 50%. LVEF will be monitored regularly according to the schedule of activities (see Section 1.3). Figure A3-1 summarizes the management of study medication in participants who develop an asymptomatic

decrease in LVEF. The decision to continue or stop study treatment should be based on two factors: measured LVEF and changes in LVEF from baseline. If a significant LVEF decrease occurs, this decrease should be confirmed by a second assessment within approximately 3 weeks that also shows a significant decrease.

Figure A3-1 Algorithm for Continuation and Discontinuation of Study Treatment



Cardiac function will be monitored during the study by ECG and ECHO or MUGA (see Section 1.3). Participants who develop symptomatic left ventricular systolic dysfunction (LVSD) should be evaluated by a certified cardiologist, and the results of this evaluation should be reported in the eCRF (Table A2-4). Symptomatic LVSD (also referred to as congestive heart failure [CHF]) will be assessed as "heart failure" on the basis of NCI CTCAE v5.0 (Table A2-2) and NYHA classification (see Table A2-3). Participants with heart failure (NYHA Class III and IV) must discontinue study treatment (Section 7.1).

CHF should be treated and monitored according to standard medical practice. If an investigator is concerned that an adverse event may be related to LVSD, an additional LVEF measurement should be performed as soon as possible and within 3 weeks of onset. Symptomatic LVSD (referred to as heart failure) should be reported as a serious adverse event. LVEF results must also be reported.

Heart failure occurring during the study and for up to 3 years after Phesgo discontinuation must be reported irrespective of causal relationship and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

Heart failure and asymptomatic LVEF decline adverse events must be graded per NCI CTCAE v5.0 and reported in the eCRF Form as described in Table A2-4.

A3–3.1.3 EGFR-Related Toxicities

A3–3.1.3.1 Diarrhea

To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication (e.g., loperamide) should be considered, and participants should be treated with fluids and electrolyte replacement, as clinically indicated.

A3–3.1.3.2 Rash/Skin Reactions

Treatment recommendations for EGFR-associated rash / skin reactions include topical or oral antibiotics, topical pimecrolimus, and topical steroids or systemic steroids (for severe reactions). These agents may be used in participants experiencing pertuzumab-related rash/skin reactions, as clinically indicated, although they have not been studied in this context.

A3–3.1.3.3 Mucositis

Mucositis is generally not considered preventable. Although for some cytotoxic agents, mucositis may be reduced by cooling the mouth using ice chips before and during the infusion.

A3–3.1.4 Management of Febrile Neutropenia/Neutropenia

Treatment emergent neutropenia may be treated with hematopoietic growth factors (e.g., granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor) as indicated by the current ASCO guidelines (Smith et al. 2015; Bohlius et al. 2019).

For any Grade 3 or 4 febrile neutropenia it would be recommended to decrease docetaxel/paclitaxel by one dose level, treat with hematopoietic growth factors, or discontinue taxane as per local clinical practice.

A3–3.2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS: GIREDESTRANT

A3–3.2.1 Dose Modifications

No dose reductions are permitted for giredestrant. See Table A3-1 for further details on management of adverse events associated with giredestrant.

A3–3.2.2 Treatment Interruption

Giredestrant may be temporarily suspended or delayed for up to 9 weeks in participants who experience toxicity considered to be related to study drug. See Table A3-1 for further details on management of adverse events associated with giredestrant.

A3–3.2.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table A3-1. Additional guidelines are provided in the subsections below.

Table A3-1 Guidelines for Management of Participants Who Experience a Giredestrant-Related Toxicity

Event	Action to Be Taken
Elevation of Hepatic Transaminases:	
General guidance	• If participant 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 cause found, consult with hepatologist. • Treat participant with hepatic enzyme elevation according to local standard of care.
Grade 1 or 2	• Continue giredestrant. • Rule out alternative etiologies (e.g., concomitant medications, or biliary obstruction). • Instigate more frequent monitoring with increased monitoring of liver function tests (at least fortnightly until resolved). • Treat participant according to local standard of care.
Grade 3	• Withhold giredestrant. • Consider consultation with hepatologist. • Once event resolves Grade ≤1, resume giredestrant at full dose with increased monitoring until the event is assessed as resolved or stable.
Grade 4 or meets criteria as defined by Hy's Law (see Section A2-7.7)	• Permanently discontinue giredestrant. • Consult with hepatologist.

Appendix 3 Safety Plan: Management of Identified and Potential Risks

Event	Action to Be Taken
Gastrointestinal Events (Nausea, Vomiting, Diarrhea)	
General guidance	• Monitor closely for gastrointestinal symptoms. If participant 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 1	• Continue giredestrant.
Grade 2	• Manage and treat according to local standard of care. • If persistent despite appropriate medical therapy, withhold giredestrant until resolution to Grade ≤1.
Grade≥ 3	• Withhold giredestrant until event resolves to Grade ≤1. • Manage and treat participant according to local standard of care. • Consider consulting with gastroenterologist. • Resume giredestrant at regular dose once the event resolves to Grade ≤1.
Venous Thromboembolic Events (Including Pulmonary Embolism)	
General guidance	• Advise participants to seek immediate medical attention if they become aware of any symptoms of pulmonary embolism or deep vein thrombosis, such as acute onset of chest pain, shortness of breath, or swelling in extremities.
Grade 1	• Continue giredestrant.
Grade≥ 2	• Withhold giredestrant until participant is stable (any thrombolytic therapy and inpatient anticoagulation has been completed). • Manage and treat participant according to local standard of care. • Resume giredestrant at full dose once the participant is stable. • Permanently discontinue giredestrant for recurrent thromboembolic events.

Event	Action to Be Taken
Bradycardia	
General guidance	• Monitor participant closely for symptomatic bradycardia. • Electrocardiogram assessment should be conducted as outlined in Section 8.2.4.
Grade 1	• Continue giredestrant. • Continue to monitor participant per schedule of activities (Section 1.3). • If heart rate falls below 40 beats per minute, withhold giredestrant until heart rate returns to > 40 beats per minute if participant remains asymptomatic.
Grade 2	• Withhold giredestrant and consult with cardiologist. • Resume giredestrant at full dose once the event improves to Grade ≤1and heart rate returns to > 40 beats per minute.
Grade ≥3	• Permanently discontinue giredestrant and consult with cardiologist.
Renal Toxicity or Increased Creatinine	
Grade 1 or 2	• Continue giredestrant. • Manage participant according to local standard of care.
Grade ≥3	• Permanently discontinue giredestrant. • Manage participant according to local standard of care. • Consult with nephrologist.
Non-Hematologic Toxicity	
Grade 1 or 2	• Continue giredestrant. • Rule out alternative etiologies.
Grade 3	• Withhold giredestrant until symptoms resolve to Grade 1 or better, and then resume giredestrant at full dose.
Grade 4	• Permanently discontinue giredestrant. Participants not thought to be at risk of further acute toxicity may be rechallenged with giredestrant following approval of the Medical Monitor.

A3–4 REFERENCES

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Smith TJ, Bohlke K, Lyman GH, et al. American Society of Clinical Oncology. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3199–212.

Appendix 4
Collection of Pregnancy Information

A4–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 7 months after the final dose of Phesgo. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant 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 or birth defect in the child) should be reported on the Adverse Event electronic Case Report Form (eCRF). In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 7 months after the final dose of Phesgo. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with

additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A4–3 ABORTIONS

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 the investigator becomes aware of the event; see Section A2–5).

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 the investigator becomes aware of the event; see Section A2–5). 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.

A4–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment 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 the investigator becomes aware of the event; see Section A2–5).

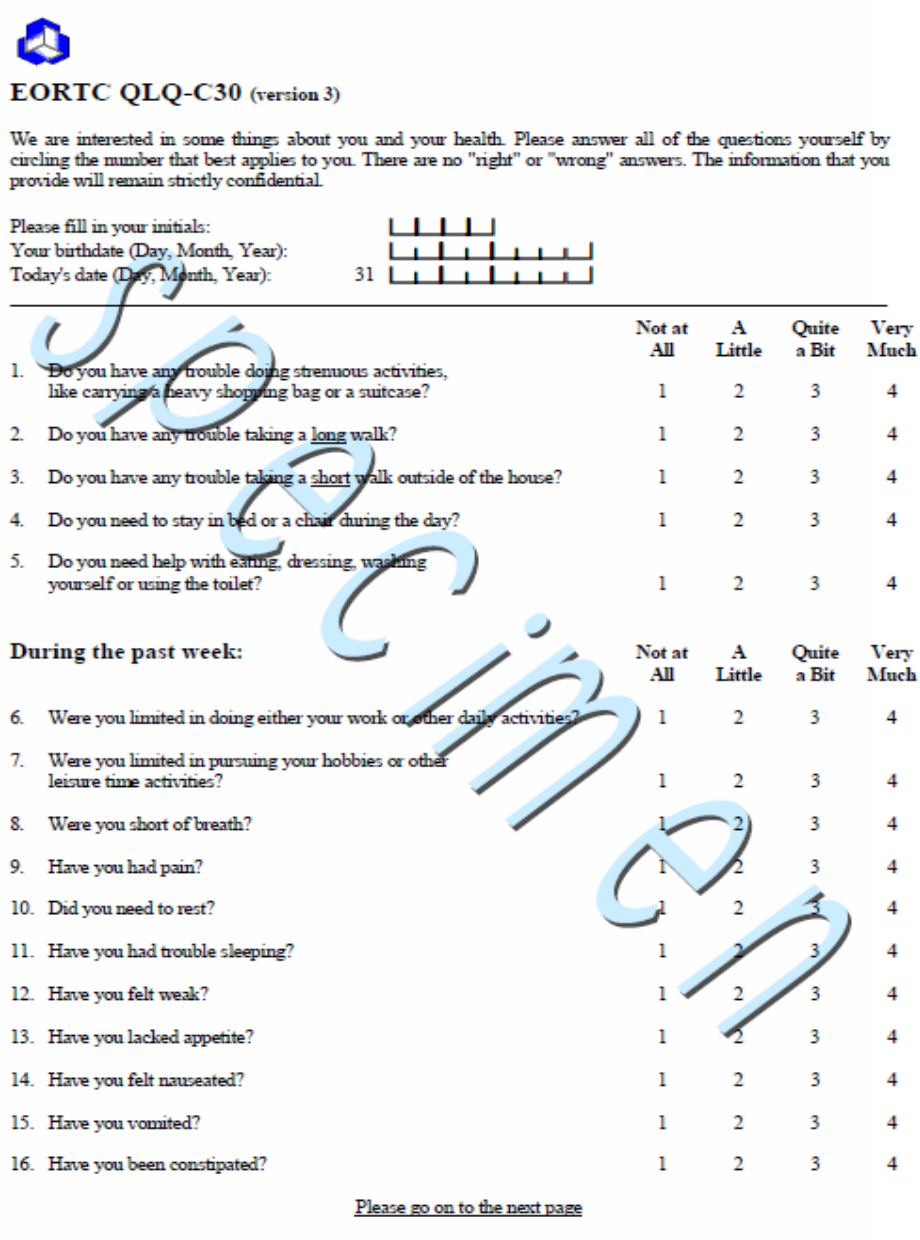
Appendix 5
Clinical Outcome Assessment Instruments

A5–1 CLINICAL OUTCOME ASSESMENT INSTRUMENT(S)

Patient-reported outcome (PRO) data will be collected from participants randomized to receive study maintenance treatment through use of the following instruments: European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life–Core 30 Questionnaire (QLQ-C30), EORTC Quality of Life–BR23 Questionnaire (QLQ-BR23), the worst pain item from the Brief Pain Inventory-Short Form (BPI-SF), select items of the PRO-CTCAE, the GP5 overall treatment side-effect bother item of the FACT-G, the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH), and the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) (assessed in that order).

A5–1.1 EORTC QLQ-C30

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

A5–1.2 EORTC QLQ BR23

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ENGLISH

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

A5–1.3 BRIEF PAIN INVENTORY-SHORT FORM (BPI-SF)

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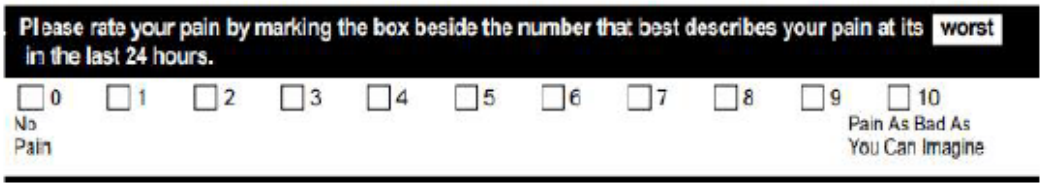
Brief Pain Inventory–Short Form (BPI-SF) "Worst Pain" Item



A5–1.4 PRO-CTCAE

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0
English
Form Created on 12 November 2021

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days...

1a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
1b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

2a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
2b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

3a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

4a. In the last 7 days, did you have any RASH?	
O Yes	O No

5a. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
5b. In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
5c. In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

6a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
6b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

7a. In the last 7 days, how OFTEN did you have HOT FLASHES/FLUSHES?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
7b. In the last 7 days, what was the SEVERITY of your HOT FLASHES/FLUSHES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

OTHER SYMPTOMS					
Do you have any other symptoms that you wish to report?					
O Yes		O No			
Please list any other symptoms:					
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe

A5–1.5 FACT-G SINGLE-ITEM GP5

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GP5 (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4

A5–1.6 WPAI:GH

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Work Productivity and Activity Impairment Questionnaire:
General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

A5–1.7 EUROQOL EQ-5D-5L

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- **I have slight problems in walking about** ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

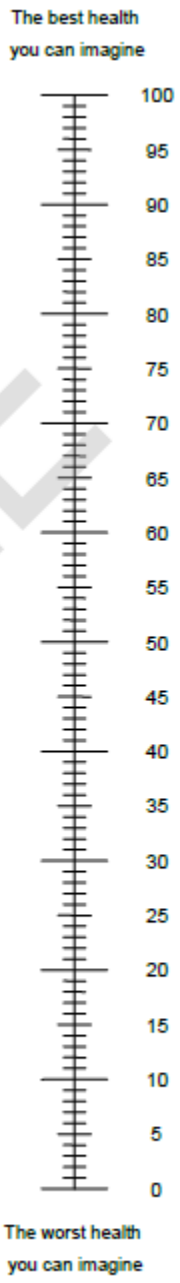
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6
Clinical Safety Laboratory Tests

The tests detailed in Table A6-1 will be performed by the local laboratory. Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Investigators must document their review of each laboratory safety report.

Table A6-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells) • Chemistry panel (serum): sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, creatine clearance (at screening only, if necessary to confirm eligibility), total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, and LDH • Coagulation: INR (or PT) and aPTT (or PTT) • FSH for premenopausal/perimenopausal participants, female participants aged <60 years, and participants (male and female) who are receiving LHRHa. *For postmenopausal patients age <60 years, this is applicable only at screening to confirm postmenopausal status (as defined in Section 5.1).* • Estradiol for premenopausal/perimenopausal participants, female participants aged <60 years, and participants (male and female) who are receiving LHRHa. *For postmenopausal patients age <60 years, this is applicable only at screening to confirm postmenopausal status (as defined in Section 5.1).* • Pregnancy test All women of childbearing potential will have a serum pregnancy test at screening within 14 days prior to initiation of induction therapy. Urine pregnancy tests will be performed at every cycle during induction therapy *(can be performed up to 3 days prior to Day 1)*, study maintenance treatment *(can be performed up to 7 days prior to Day 1)*, at the treatment discontinuation visit, and *monthly* at Months 1 to 7 after the final dose of Phesgo. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood)

Appendix 7
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area (e.g., brain metastases) or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with prior studies, if possible. Each case should be discussed with the

radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, because the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally

used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to $<$ 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of $<$ 10 mm.

Recent literature indicates that vaccination-related adenopathy (enlarged lymph nodes) on radiologic imaging (e.g., CT, MRI) and transient uptake on PET scan are frequent findings (up to 16% in vaccine trials) after administration of COVID-19 vaccines. These findings may appear similar to malignant nodal involvement and hence impact image interpretation.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well, and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short

axis $<$ 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to $<$ 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of $\geq$ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A7-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A7-1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table A7-2 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the

individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A7-1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 8
Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

Appendix 9
Genetics: Use and Analysis of DNA for Mandatory Samples

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to Phesgo and giredestrant in ER-positive, HER2-positive BC and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to Phesgo and giredestrant and treatments of this drug class /or treatments of this drug class and ER-positive, HER2-positive. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

Samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or whole exome sequencing (WES) to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to Phesgo and giredestrant or study treatments of this class to understand the study disease or related conditions.

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on Phesgo and giredestrant continues but no longer than 5 years or other period as per local requirements.

Appendix 10
Relative Cardiotoxicities of Anthracycline: A Comparison of Relative Toxicities of Different Cardiotoxic Drugs and Dosage Schedules

Adapted from Table 134-3, Kufe DW, Frei E III, Holland JF, et al., ediotors. Holland-Frei Cancer Medicine. 7th ed. Columbia: BC Decker Inc. 2006.

Drug	Schedule	Cardiotoxicity Index Compared with Doxorubicin Administered by Standard Schedule [a]	Recommended Maximum Dose (mg/m^2) [b]
Doxorubicin	Rapid infusion (20 min)	1	400
Doxorubicin	Weekly	0.73	550
Doxorubicin	24-h infusion	0.73	550
Doxorubicin	48-h infusion	0.62	—
Doxorubicin	96-h infusion	0.5	800–1000 [c]
Epirubicin	Rapid infusion	0.44	900
Mitoxantrone	Rapid infusion	2.5	160
Daunorubicin	Rapid infusion	0.5 [d]	800 [d]
Idarubicin	Rapid infusion	2.67	150
Pirarubicin	Rapid infusion	0.62	650

[a] Derived by dividing 400 mg/m^2, the recommended maximum dose of rapid-infusion doxorubicin, by the recommended maximum dose for the agent in question. The cardiotoxicity index represents a factor by which to multiply the cumulative dose of a drug administered to obtain an approximation of toxicity that might be expected had the resultant amount of doxorubicin been given by rapid infusion. For example, if a cumulative dose of 120 mg/m^2 of mitoxantrone had been administered, the patient would be expected to demonstrate cardiac damage approximately equal to 300 mg/m^2 of doxorubicin given by rapid infusion ($120 \times 2.5 = 300$). This value is useful when changing from one cardiotoxic regimen to another. When the sum of the products for the indexes and the cumulative doses administered exceeds 400 mg/m^2, the risk of clinically significant cardiotoxicity exceeds 5%.

[b] Dose producing clinically significant congestive heart failure in 5% of patients.

[c] Less toxic by endomyocardial biopsy.

[d] Inadequate data.

Appendix 11
Investigational, Non-Investigational, and Auxiliary Medicinal Product Designations (for Use in United Kingdom and European Economic Area)

Table A11-1 IMP/NIMP Designation (for Use in U.K.)

Product Name	IMP/NIMP Designation	Marketing Authorization Status in U.K.	Used within Marketing Authorization
Phesgo (RO7198574)	IMP (test product) [a]	Approved	No [b]
Giredestrant (RO7197597)	IMP (test product)	Not approved	Not applicable
Docetaxel	NIMP (background therapy)	Approved	Yes
Paclitaxel	NIMP (background therapy)	Approved	Yes
Tamoxifen	NIMP (other)[c]	Approved	Yes
Anastrozole	NIMP (other)[c]	Approved	Yes
Letrozole	NIMP (other)[c]	Approved	Yes
Exemestane	NIMP (other)[c]	Approved	Yes
LHRHa	NIMP (other)[d]	Not applicable [e]	Not applicable [e]

AI = aromatase inhibitor; ET = endocrine therapy; IMP=investigational medicinal product; LHRHa=luteinizing hormone–releasing hormone agonist; NIMP=non-investigational medicinal product.

[a] Phesgo qualifies as both test product and comparator.

[b] Phesgo in combination with giredestrant is not approved in the U.K.

[c] Optional ET (tamoxifen or AIs: anastrozole, letrozole, or exemestane) does not fall within the definition of IMP. ET is considered standard of care.

[d] LHRHa does not fall within the definition of IMP, and is therefore classified as NIMP. Pre- and perimenopausal women or men who receive an AI must also receive a LHRHa, and those who receive tamoxifen may also receive LHRHa. Pre- and perimenopausal women, and men will receive LHRHa with giredestrant. Acceptable agents include, but are not limited to: leuprolide acetate, goserelin acetate, and triptorelin pamoate

[e] LHRHa is a class of medicine and not an individual product. Therefore, this field is not applicable. The sponsor expects that appropriate LHRHa is given as standard treatment per local practice

Table A11-2 IMP/AxMP Designation (for Use in EEA)

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Phesgo (RO7198574)	IMP (test product) [a]	Approved	No [b]
Giredestrant (RO7197597)	IMP (test product)	Not approved	Not applicable
Docetaxel	AxMP (background therapy)	Approved	Yes
Paclitaxel	AxMP (background therapy)	Approved	Yes
Tamoxifen	AxMP (other) [c]	Approved	Yes
Anastrozole	AxMP (other) [c]	Approved	Yes
Letrozole	AxMP (other) [c]	Approved	Yes
Exemestane	AxMP (other) [c]	Approved	Yes
LHRHa	AxMP (other) [d]	Not applicable [e]	Not applicable [e]

AI = aromatase inhibitor; AxMP = auxiliary medicinal product; EEA = European Economic Area; ET = endocrine therapy; IMP=investigational medicinal product; LHRHa =luteinizing hormone–releasing hormone agonist.

[a] Phesgo qualifies as both test product and comparator.

[b] Phesgo in combination with giredestrant is not approved in the EU.

[c] Optional ET (tamoxifen or AIs: anastrozole, letrozole, or exemestane) does not fall within the definition of IMP in Regulation 536/2014, and is therefore classified as AxMP. ET is considered standard of care.

[d] LHRHa does not fall within the definition of IMP in Regulation 536/2014, and is therefore classified as AxMP. Pre- and perimenopausal women or men who receive an AI must also receive a LHRHa, and those who receive tamoxifen may also receive LHRHa. Pre- and perimenopausal women, and men will receive LHRHa with giredestrant. Acceptable agents include, but are not limited to: leuprolide acetate, goserelin acetate, and triptorelin pamoate

[e] LHRHa is a class of medicine and not an individual product. Therefore, this field is not applicable. The sponsor expects that appropriate LHRHa is given as standard treatment per local practice.

Appendix 12
Protocol Amendment History

PROTOCOL AMENDMENT, VERSION 2: 19 MAY 2022

Protocol WO43571 has been amended to align with guidelines, to provide additional clarifications, and to correct inconsistencies. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- Section 1.3 Schedule of Activities footnote 'k' has been updated to increase the frequency of pregnancy testing to monthly during Follow Up Month 1 to Month 7 (exposure period of study drug), as per CTFG guidelines.
- An exclusion criteria around serious COVID-19 infection has been added to Section 5.2 to align with wording in Section 2.3.1.
- Section 6.1 has been updated to clarify the need for a loading dose of Phesgo if the time between doses is ≥6 weeks.
- Febrile neutropenia and neutropenia have been added as a risk of administration of Phesgo, and the associated guidance on how to manage these events have been added (Appendix A3-1 and A3-3.1).
- Section 1.3 Schedule of Activities footnote 'm' has been updated to align with Section 4.1.3 and clarify that all men, as well as pre- and perimenopasual women in Arm A should receive LHRHa if they are receiving endocrine therapy.
- Table 5 has been updated to align with Section 8.8 and clarify that ADA sampling is required at the treatment discontinuation visit.
- Section 6.4 has been updated to include the training of the patient on the handling and administration of giredestrant, including the use of a patient diary. Guidance has also been provided on drug accountability and how to record this information in the eCRF.
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 8.10.2.6)

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

Appendix 13
Abbreviations

Abbreviation or Term	Definition
ABC	advanced breast cancer
ACE	angiotensin-converting enzyme
ADA	anti-drug antibody
AI	aromatase inhibitor
ARDS	acute respiratory distress syndrome
ARR	administration-related reaction
ASCO	American Society of Clinical Oncology
AV	atrioventricular
AxMP	auxiliary medicinal product
BC	breast cancer
BICR	blinded independent central review
BPM	beats per minute
CAP	College of American Pathologists
CBR	clinical benefit rate
CCOD	clinical cutoff date
CHF	congestive heart failure
CI	confidence interval
COVID-19	coronavirus disease 2019
CR	complete response
CRF	Case Report Form
CT	computed tomography (scan)
ctDNA	circulating tumor DNA
ddAC	dose-dense doxorubicin plus cyclophosphamide
DDI	*drug-drug interaction*
DOR	duration of response
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EORTC	*European Organisation for Research and Treatment of Cancer*
EuA	emergency use authorization

Appendix 13 Abbreviations

Abbreviation or Term	Definition
ER	estrogen receptor
ET	endocrine therapy
FACT-G	*Functional Assessment of Cancer Therapy–General*
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle-stimulating hormone
GHS/QoL	global health status/ quality of life
HBsAg	*hepatitis B surface antigen*
HBV	*hepatitis B virus*
HCV	*hepatitis C virus*
HER2	HER2, human epidermal growth factor receptor 2
HGRAC	Human Genetics Resources Administration of China
HR	Hazard ratio
IE	intercurrent event
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IM	Intramuscular
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRC	Independent Review Committee
ISH	in situ hybridization
LBD	ligand-binding domain
LHRHa	luteinizing hormone-releasing hormone agonist
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MAPK	mitogen-activated protein kinase
MBC	metastatic breast cancer

Appendix 13 Abbreviations

Abbreviation or Term	Definition
MN	mobile nurse
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NPT	non-protocol anti-cancer treatment
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PH	Perjeta and Herceptin IV/SC
PK	pharmacokinetic
PI3K	phosphoinositide 3-kinase
PO	by mouth; orally
PgR	progesterone receptor
PR	partial response
PRO	*patient*-reported outcome
Q3W	every 3 weeks
QD	every day
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SERD	selective estrogen receptor degrader
SERM	selective estrogen receptor modulators
ULN	upper limit of normal

Appendix 13 Abbreviations

Abbreviation or Term	Definition
WES	whole exome sequencing
WGS	whole genome sequencing