Official Title: A Phase IIIB, Multinational, Multicenter, Randomized, Open-Label Study to Evaluate Patient Preference for Home Administration of Fixed-Dose Combination of Pertuzumab and Trastuzumab for Subcutaneous Administration in Participants with Early or Locally Advanced/Inflammatory HER2-Positive Breast Cancer

NCT Number: NCT05415215

Document Date: Protocol Version 3: 25-Jan-2024

PROTOCOL

PROTOCOL TITLE:	**A PHASE IIIB, MULTINATIONAL, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE PATIENT PREFERENCE FOR HOME ADMINISTRATION OF FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB FOR SUBCUTANEOUS ADMINISTRATION IN PARTICIPANTS WITH EARLY OR LOCALLY ADVANCED/ INFLAMMATORY HER2-POSITIVE BREAST CANCER**
PROTOCOL NUMBER:	MO43110
STUDY NAME:	ProHer
VERSION NUMBER:	*3*
TEST *PRODUCTS*:	Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous (PH FDC SC) administration (RO7198574) Pertuzumab IV (RO4368451) Trastuzumab IV (RO45-2317) Trastuzumab emtansine IV (RO5304020)
STUDY PHASE:	Phase IIIb
REGULATORY AGENCY *IDENTIFIERS*:	IND Number: Not applicable EudraCT Number: 2021-002346-33 *EU CT Number: 2023-506380-33-00* NCT Number: NCT05415215

SPONSOR'S 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	*15 November 2022*
1	02 February 2022

PROTOCOL AMENDMENT, VERSION 3

RATIONALE

Protocol MO43110 has been amended to align with the requirements for E.U. Clinical trials Regulation No 536/2014. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The EU CT number has been added to the protocol/synopsis title pages.
- A new table summarizing several key aspects of the trial has been added to the synopsis.
- Text describing cardiac assessments has been revised to clarify the timing of the assessments and to indicate that the investigator may request additional assessment based on the individual participant's cardiovascular function (Tables 1–4, Section 1.3; Section 8.2.4, Appendix 19).
- New footnotes have been added to the Schedule of Activities (SoAs) for the neoadjuvant phase to indicate that the randomization and the Day 1, Cycle 1 visit should take place within 3 days of the screening visit and that the timing of the pre-surgery mammography and ECG assessments should be as per local practice /guidance (Tables 1–3, Section 1.3).
- Footnote ‘q’ in the SoAs for the neoadjuvant phase has been updated to indicate that the assessment of hematology / limited biochemistry prior to surgery can be done as per local clinical practice; however, the results must be available prior to the surgery (Tables 1–3, Section 1.3).
- Footnote ‘n’ in the SoA Table 2 and 3 has been revised to match the text describing tumor assessment in SoA Table 1 footnote ‘n’ (Table 2 and 3, Section 1.3).
- Footnote w in the SoA Table 3 has been updated to indicate that the time period between Cycle 4 and Cycle 5 can be either 2 or 3 weeks, as per local practice or investigator discretion. (Table 3, Section 1.3).
- The SoA for the adjuvant phase has been split into two tables: Table 4 should be used for participants in Arms C or D (Adjuvant treatment period – PH FDC SC) and Table 5 should be used for participants in Arm E (Adjuvant treatment period – Trastuzumab emtansine IV) (Section 1.3).
- A footnote has been added to the SoA table row describing the Hematology / limited biochemistry assessments for Arm C and D during the adjuvant phase to indicate that these assessments at cycle 9 may be done within 3 days prior to treatment day (within the hospital) for participants who selected to be treated at home during the treatment continuation period (Table 4, Section 1.3). The wording of this footnote has also been clarified.
- A footnote has been added to Table 5 to indicate that trastuzumab emtansine cannot be initiated if the platelet count is $<$100,000/μL at Cycle 1. Trastuzumab emtansine has not been studied in patients with platelet counts $<$100,000/μL prior to initiation of treatment (Table 5, Section 1.3).

- Text has been expanded to clarify that limited physical examinations may be conducted by a mobile HCP as clinically indicated and in accordance with institutional practice or the American Cancer Society/American Society of Clinical Oncology Breast Cancer (ACS/ASCO) Breast Cancer Survivorship Care Guideline (Footnote ‘g’ in SoA Table 4, Section 1.3, and Section 8.2.1).
- Text has been revised to clarify that the ‘baseline’ patient weight used to determine if subsequent doses of trastuzumab emtansine should be adjusted is the baseline weight after surgery (and not screening as previously stated) (Footnote ‘i’ in SoA Table 5, and Section 6.1.3).
- A new secondary endpoint investigating the patient’s choice of setting for the treatment continuation period has been added (Section 3).
- The text describing treatment during the adjuvant phase has been revised to better differentiate between treatment for participants who have achieved pCR after surgery and participants who have residual disease after surgery (Section 4.1.2).
- The guidance on the post-surgery radiotherapy, including its timing, has been clarified (Section 4.1.2.2 and Section 6.8.2).
- The use of hormonal contraceptives is now prohibited regardless of the hormone receptor status. Inclusion criteria and the list of prohibited therapies have been updated (Sections 5.1.1 and 6.8.4).
- Non-investigational medicinal products have been renamed auxiliary medicinal products (AxMPs) (Sections 6, 6.1, 6.1.4, 6.1.5, and 6.1.6).
- The tumor disease staging descriptions of ‘operable’ and ‘locally advanced’ used for patient stratification have been updated (Section 6.3.1).
- Text describing regulatory reporting requirements for serious adverse events has been updated (Section 8.3.4).
- Text describing the provision of Medical Monitor contact information and the Emergency Medical Call Centre has been revised for clarity (Section 8.3.9).
- The description of the statistical analyses has been updated to clarify that all data in this study will be analyzed in a descriptive manner (Section 9.4.1).
- Reasons for terminating the study have been added to the protocol (Section A1–9).
- The guidance for recording injection/infusion reactions, diagnoses vs signs and symptoms, and special situations (accidental overdose and/or medication error) have been restructured for clarity (Section A2–7.1 and A2–8).
- Minor edits have been made to the Health Care Professional Questionnaires for clarity (Appendices 6, 7, 9, and 10).
- Text describing the pulmonary toxicity and hematologic toxicity associated with trastuzumab emtansine (Sections A3–6.1 and A3–6.5) and the text describing the management of participants who experience pulmonary or hematologic toxicities during treatment with trastuzumab emtansine (Section A3–9.2) has been updated to align to the Kadcyla Investigator Brochure, v17.

- A new Appendix has been added describing the designations of the Investigational and Auxiliary Medicinal Products (Appendix 20).

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE IIIB, MULTINATIONAL, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE PATIENT PREFERENCE FOR HOME ADMINISTRATION OF FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB FOR SUBCUTANEOUS ADMINISTRATION IN PARTICIPANTS WITH EARLY OR LOCALLY ADVANCED/ INFLAMMATORY HER2-POSITIVE BREAST CANCER**
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TEST *PRODUCTS*:	Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous (PH FDC SC) administration (RO7198574) Pertuzumab IV (RO4368451) Trastuzumab IV (RO45-2317) Trastuzumab emtansine IV (RO5304020)
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 as instructed by your local study monitor.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE IIIB, MULTINATIONAL, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE PATIENT PREFERENCE FOR HOME ADMINISTRATION OF FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB FOR SUBCUTANEOUS ADMINISTRATION IN PARTICIPANTS WITH EARLY OR LOCALLY ADVANCED/ INFLAMMATORY HER2-POSITIVE BREAST CANCER**
REGULATORY AGENCY IDENTIFIERS:	*IND Number: Not applicable* *EudraCT Number: 2021-002346-33* *EU CT Number: 2023-506380-33-00* *NCT Number: NCT05415215*

Study Rationale

The purpose of this study is to evaluate the patient-reported preference for the pertuzumab and trastuzumab (PH) fixed-dose combination (FDC) for subcutaneous (SC) administration (PH FDC SC) in the home setting compared with the hospital setting in participants with early or locally advanced/inflammatory human epidermal growth factor receptor 2-positive (HER2+) breast cancer.

The SC delivery of biotherapeutics is well-established as a route of administration that is effective and well-tolerated across many therapeutic areas (Collins et al. 2020). It can offer several advantages over intravenous (IV) administration, including the convenience of self-administration, improved patient experience, reduced treatment burden and lower healthcare costs.

Moreover, the reduction in hospital time of the patient will reduce the patient's exposure to nosocomial pathogens and reduce the burden on healthcare systems.

Objectives and Endpoints

This study will evaluate the patient-reported preference of PH FDC SC administration in the home setting compared with the hospital setting during the cross-over period of adjuvant treatment in participants with early or locally advanced/inflammatory HER2+ breast cancer.

The administration of PH FDC SC in the home setting will be conducted by healthcare professionals (HCPs).

Specific primary and secondary objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
• To evaluate patient preference of PH FDC SC administration in the home setting during the cross-over period of the adjuvant phase of the study	• Proportion of participants who preferred the administration of PH FDC SC in the home setting compared with the hospital setting in Question 1 of Patient Preference Questionnaire (PPQ) (Appendix 5)

Secondary Objectives	Corresponding Endpoints
• To evaluate the perception of HCPs of time/resource use and convenience of PH FDC SC compared to pertuzumab IV and trastuzumab IV (P+H IV) during the neoadjuvant phase of the study	• Responses of HCPs to the Healthcare Professional Questionnaire (HCPQ) by individual questions in the neoadjuvant phase (Appendix 6 and Appendix 7)
• Collect pathologic complete response (pCR) data post-surgery	• Proportion of participants achieving pCR, defined as eradication of invasive disease in the breast and axilla (i.e., ypT0/Tis ypN0), according to local pathologist assessment following the AJCC criteria (FDA 2020)
• To evaluate Health-related Quality of Life (HRQoL) during the neoadjuvant phase of the study	• HRQoL assessed by EORTC QLQ-C30 scores in the neoadjuvant phase (Appendix 8)
• To evaluate HRQoL with PH FDC SC administered during the adjuvant phase of the study	• HRQoL assessed by EORTC QLQ-C30 scores in the participants treated with PH FDC SC during the adjuvant phase (Appendix 8)
• To evaluate the perception of HCPs of time/resource use of PH FDC SC during the adjuvant cross-over period	• Responses of HCPs to the HCPQ by individual questions in the adjuvant cross-over period (Appendix 9 and Appendix 10)
• To evaluate HRQoL for participants treated with trastuzumab emtansine IV during the adjuvant phase	• HRQoL assessed by EORTC QLQ-C30 scores in the participants treated with trastuzumab emtansine IV during the adjuvant phase (Appendix 8)
• *To evaluate patient's choice of setting for the treatment continuation period*	• *Proportion of participants who selected the administration of PH FDC SC in the home setting compared with the hospital setting in the treatment continuation period*
Secondary Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of PH FDC SC and P+H IV during the neoadjuvant phase of the study	• Incidence, nature and severity of all adverse events (AEs), Grade ≥ 3 AEs, SAEs, and cardiac AEs (including left ventricular ejection fraction [LVEF] events) with severity determined according to National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) v5.0 (Appendix 14 and Appendix 16) • Incidence of premature withdrawal from the neoadjuvant treatment with PH FDC SC and P+H IV • Targeted vital signs and physical findings • Targeted clinical laboratory test results
• To evaluate the safety and tolerability of PH FDC SC administered in the home setting and hospital setting during the cross-over period and the entire adjuvant treatment period	• Incidence, nature, and severity of all AEs, Grade ≥ 3 AEs, SAEs, and cardiac AEs (including LVEF events) with severity determined according to NCI CTCAE v5.0 (Appendix 14 and Appendix 16) • Incidence of premature withdrawal from the adjuvant treatment with PH FDC SC

	• Targeted vital signs and physical findings • Targeted clinical laboratory test results
• To evaluate the safety and tolerability of trastuzumab emtansine IV during the adjuvant phase of the study	• Incidence, nature, and severity of all AEs, Grade ≥ 3 AEs, SAEs, and cardiac AEs (including LVEF events) with severity determined according to NCI CTCAE v5.0 (Appendix 14 and Appendix 16) • Incidence of premature withdrawal from the treatment with trastuzumab emtansine IV • Targeted vital signs and physical findings • Targeted clinical laboratory test results

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HCP = healthcare professional; HCPQ = Healthcare Professional Questionnaire; IV = intravenous; LVEF = Left ventricular ejection fraction; NCI = National Cancer Institute; pCR = pathologic complete response; PPQ = Patient Preference Questionnaire; SAE = serious adverse event.

Overall Design

This is a phase IIIb, multinational, multicenter, randomized, open-label study to evaluate the patient preference of PH FDC SC administration in the home setting compared with the hospital setting during the cross-over period of adjuvant treatment in participants with early or locally advanced/inflammatory HER2+ breast cancer.

This study will consist of two phases.

1. During the neoadjuvant phase, participants will be randomized in a 1:2 ratio to receive treatment in the hospital with either P+H IV plus chemotherapy (Arm A) or PH FDC SC plus chemotherapy (Arm B). Participants in both cohorts are scheduled to undergo surgery after the completion of neoadjuvant therapy. This could be after 6 or 8 cycles depending on the chosen neoadjuvant scheme.

   After surgery, local pathologists interpreting surgical specimens will determine whether pCR has been achieved following the AJCC criteria (FDA 2020).

2. During the adjuvant phase, participants who achieve pCR after surgery will be treated with 2 cycles of PH FDC SC in the hospital. Then, participants will be randomized in a 1:1 ratio to two treatment arms in a cross-over manner, Arm C (3 cycles of PH FDC SC treatment in the hospital followed by another 3 cycles of PH FDC SC treatment in the home setting) and Arm D (3 cycles of PH FDC SC in the home setting followed by 3 cycles of PH FDC SC in the hospital). To complete a total of 18 cycles of treatment with pertuzumab and trastuzumab in the (neo)adjuvant setting, the last cycles of PH FDC SC will be administered in the hospital or in the home setting, as selected by the participant at the end of cross-over period.

   Participants can request to change from home administration to hospital administration (and vice-versa) during the treatment continuation period, but not during the treatment cross-over period. This change can occur once only.

   Participants with pathologic evidence of residual invasive carcinoma in the breast or axillary lymph nodes following completion of preoperative therapy and surgery will be treated with trastuzumab emtansine for 14 cycles (Arm E). Trastuzumab emtansine will be administered IV in the hospital as per prescribing information.

A study schema is provided in Section 1.2 (see Figure 1). The schedules of activities are provided in Section 1.3 (see Table 1, Table 2, Table 3, Table 4, and Table 5).

This is an interventional study with randomized, parallel and crossover groups in two phases. There are a total of five arms within this study all of which are open-label.

Several key aspects of the study design and study population are summarized below.

Phase:	*Phase IIIb*	***Population Type:***	*Adult patients*
Control Method:		***Population Diagnosis or Condition:***	*HER2+ early or locally advanced/inflammatory breast cancer*
Interventional Model:	*Randomized, open-label, cross-over design*	***Population Age:***	*≥ 18 years*
Test Product{s}:	*Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous (PH FDC SC) administration (RO7198574)* *Pertuzumab IV (RO4368451)* *Trastuzumab IV (RO45-2317)* *Trastuzumab emtansine IV (RO5304020)*	***Site Distribution:***	*Multinational, multicenter*
Active Comparator:	*Not applicable*	***Study Treatment Assignment Method:***	*Randomization and stratification*
Number of Arms:	*2 (neoadjuvant phase) and 3 (adjuvant phase)*	***Number of Participants to Be Enrolled:***	*Approximately 330 participants will be enrolled for the neoadjuvant phase of study treatment such that approximately 150 evaluable participants enter Arm C and D and complete the cross-over period.*

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled unless otherwise specified by the protocol.

Study Treatment

The investigational medicinal products (IMPs) for this study are:

- Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration (PH FDC SC)
- Pertuzumab IV
- Trastuzumab IV
- Trastuzumab emtansine IV

Duration of Participation

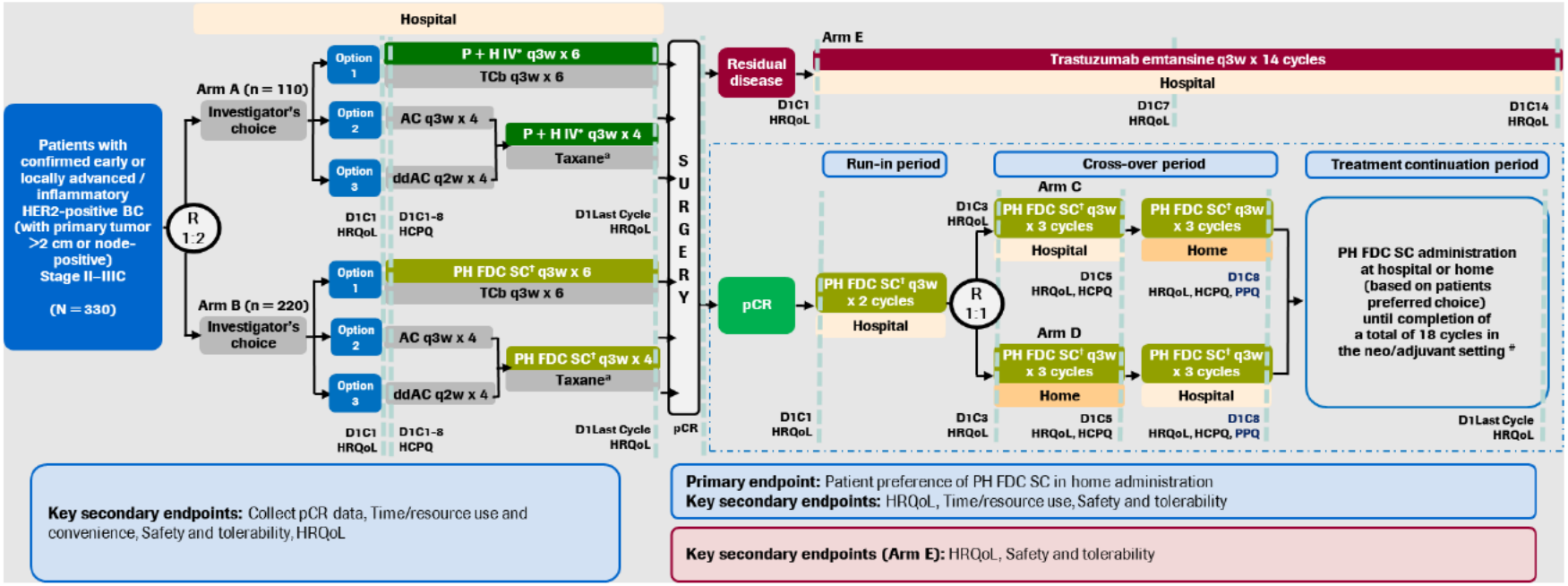
The total duration of study participation for each individual is expected to be approximately 1.5 to 2 years.

Committees

Independent Committees:	*Not applicable*
Other Committees:	*Internal Monitoring Committee (IMC)*

1.2 STUDY SCHEMA

Figure 1 Study Schema



AC = doxorubicin plus cyclophosphamide; P = pertuzumab; H = trastuzumab (Herceptin); T = docetaxel; Cb = carboplatin; ddAC = dose-dense doxorubicin plus cyclophosphamide; PH FDC SC = pertuzumab and trastuzumab fixed-dose combination for subcutaneous use; PPQ = Patient Preference Questionnaire; HRQoL = Health-related Quality of Life; HCPQ = Healthcare Professional Questionnaire; IV = intravenous; SC = subcutaneous; pCR = pathologic complete response (ypT0/Tis ypN0).

* Pertuzumab is given as a fixed dose of 840 mg IV loading dose and 420 mg IV for subsequent doses. Trastuzumab is given as an 8 mg/kg IV loading dose and 6 mg/kg IV for subsequent doses. Participants may change from P+H IV (Arm A) treatment to PH FDC SC (Arm B) treatment, in exceptional circumstances and as per investigator discretion. As such, these participants will continue on the study with the planned neoadjuvant and adjuvant phase of the study. Participants requesting to change from PH FDC SC to P+H IV in the neoadjuvant phase will be discontinued from the study. As such, these participants will be treated as per standard of care.

† PH FDC SC is given as a fixed dose. A loading dose of 1200 mg pertuzumab and 600 mg trastuzumab is then followed by 600 mg pertuzumab and 600 mg trastuzumab. [a] Taxane: docetaxel q3w x 4 or paclitaxel qw x 12. # Participants can request to change from home administration to hospital administration (and vice-versa) during the treatment continuation period, but not during the treatment cross-over period. This change can occur once only.

Hospital: any care level facilities with Oncology services, other than primary, can be public or private (clinic).

In participants receiving P + H IV or PH FDC SC with ≥ 6 weeks since their last dose, administer P+H IV or PH FDC SC as an initial dose (loading dose).

The surgery cannot be performed ≤ 2 weeks from the last systemic neoadjuvant therapy and must be performed ≤ 6 weeks after the last systemic neoadjuvant therapy.

If surgery is significantly delayed (>42 days since the last P+H IV or PH FDC SC administration), a maximum of two additional cycles of P+H IV or PH FDC SC (depending on the treatment arm (A or B) assigned to the participant at randomization), can be administered at the investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. See Appendix 18 for details of the assessments that should be conducted for participants who require additional cycles of P+H IV or PH FDC SC due to a delay with surgery.

The study treatment PH FDC SC cannot be initiated within ≤ 2 weeks of surgery but must be initiated ≤ 9 weeks from the last administration of systemic neoadjuvant therapy. Trastuzumab emtansine cannot be initiated within ≤ 2 weeks of surgery but must be initiated ≤ 6 weeks of surgery.

1.3 SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities for Neoadjuvant Phase: Treatment Option 1

		Neoadjuvant treatment period – Treatment Option 1 TCb q3w x 6 plus HER2-targeted therapy							
		3-week cycles							
Cycle	Screening [a]	1	2	3	4	5	6	Surgery [b]	Treatment discontinuation [z]
Day	–28 to –1	1	1	1	1	1	1	1	
Informed consent [c]	x								
Medical history and demographics	x								
Complete physical examination [d] [e]	x	x					x		x
Local HER2 and hormone receptor status (HER2, ER, PgR) [f]	x								
Limited physical examination [d] [g]			x	x	x	x			
Vital signs [d] [h]	x	x	x	x	x	x	x		x
ECOG Performance Status [d] [i]		x [j]				x		x (Prior surgery)	x
Height [d]	x								
Weight [d] [k]	x	x	x	x	x	x	x		x
Tumor staging [l]	x								
Bilateral mammogram (or another imaging method as per local practice) [m]	x							x (Prior surgery)	x
Clinical tumor assessment / breast examination [d] [n]	x	x	x	x	x	x	x		x
ECG (12-lead)	x				x			x *[aa]* (Prior surgery)	
LVEF (ECHO or MUGA) [o]	x					x [p]			x
Hematology / limited biochemistry [q]	x	x [j]	x	x	x	x	x	x (Prior surgery)	x

		Neoadjuvant treatment period – Treatment Option 1 TCb q3w x 6 plus HER2-targeted therapy							
		3-week cycles							
Cycle	Screening [a]	1	2	3	4	5	6	Surgery [b]	Treatment discontinuation [z]
Day	–28 to –1	1	1	1	1	1	1	1	
Pregnancy test [r]	x			x			x		x
HIV, HBV, and HCV serology	x								
HCPQ-Drug Preparation Area (Questions 1a–1b) - Appendix 6		x	x	x	x	x	x		
HCPQ-Drug Preparation Area (Questions 2–4) - Appendix 6							x		
HCPQ-Administering Treatment (Questions 1a–1g) - Appendix 7		x	x	x	x	x	x		
HCPQ-Administering Treatment (Questions 2–11) - Appendix 7							x		
EORTC QLQ-C30 - Appendix 8 [s]		x					x		
Arm A – P+H IV [t] (q3w x 6)		x (Loading dose)	x	x	x	x	x		
Arm B – PH FDC SC [u] (q3w x 6)		x (Loading dose)	x	x	x	x	x		
Docetaxel (q3w x 6) [v]		x	x	x	x	x	x		
Carboplatin (q3w x 6) [v]		x	x	x	x	x	x		
pCR post-surgery								x [w]	
Adverse events [x]	x	All adverse events and serious adverse events							
Concomitant medication [y]	x	Continuous							

Cb = carboplatin; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; HBV = hepatitis B virus; HCV = hepatitis C virus; HCPQ = healthcare professional questionnaires; HIV = human immunodeficiency virus; IV = Intravenous; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition (scan); pCR = pathologic complete response; PgR = progesterone receptor; SAE = serious adverse event; T = docetaxel.

Note: Unless otherwise specified, assessments should be performed within three days of the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. For all protocol-mandated study visits, a time window of ± 3 days is allowed. If a protocol mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date. Unscheduled visits may be performed if clinically indicated. The following assessments should be performed at a minimum: concomitant medications, adverse events, and vital signs. Additional assessments may be performed as clinically indicated, per investigator discretion. Participants may change from P+H IV (Arm A) treatment to PH FDC SC (Arm B) treatment, in exceptional circumstances and as per investigator discretion. As such, these participants will continue on the study with the planned neoadjuvant and adjuvant phase of the study. Participants requesting to change from PH FDC SC to P+H IV in the neoadjuvant phase will be discontinued from the study. As such, these participants will be treated as per standard of care.

If participants discontinue from study treatment early, they will be asked to return to the clinic for a treatment completion / treatment discontinuation visit 28 days (± 7 days) after the final dose of study drug (see Table 4 for additional details).

a Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within 28 or 7 days of randomization (as indicated) may be used; such tests do not need to be repeated for screening. Individuals who do not meet the criteria for participation in this study may qualify for one re screening opportunities (for a total of two screenings per individual) at the investigator's discretion, as described in Section 5.4. *Randomization and the Day 1, Cycle 1 visit should take place within 3 days of the screening visit.*

b The surgery cannot be performed ≤ 2 weeks from the last systemic neoadjuvant therapy and must be performed ≤ 6 weeks after the last systemic neoadjuvant therapy. If surgery is significantly delayed (>42 days since the last P+H IV or PH FDC SC administration), a maximum of two additional cycles of P+H IV or PH FDC SC (depending on the treatment arm (A or B) assigned to the participant at randomization), can be administered at the investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. See Appendix 18 for details of the assessments that should be conducted for participants who require additional cycles of P+H IV or PH FDC SC due to a delay with surgery. PH FDC SC cannot be initiated within ≤ 2 weeks of surgery but must be initiated ≤ 9 weeks from the last administration of systemic neoadjuvant therapy.

c Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

d Assessment may be done within 3 days prior to the treatment day.

e Complete physical examinations should include physical measurements (body weight in kilograms and height in centimeters) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions CRF.

f Results of previous HER2/hormone receptor status diagnoses can be used to determine eligibility if the sample was tested in the 90 days prior to enrollment. Reassessment of HER2/hormone receptor status is not mandatory in these cases but can be done as per local decision. Hormone receptor-positive participants are to be prescribed endocrine therapy according to the local guidelines after completion of pre-operative chemotherapy and surgery. Endocrine therapy will be obtained locally by the investigational sites or will be provided by the Sponsor as per country requirements.

g Limited physical examinations are symptom-directed and, in addition to the scheduled examinations indicated, may be conducted by a mobile HCP as clinically indicated. New or worsened clinically significant abnormalities observed post-screening should be recorded as AEs on the Adverse Event electronic form. After the End of Treatment, physical examinations should be conducted by treating physician in accordance with institutional practice or the American Cancer Society/American Society of Clinical Oncology Breast Cancer (ACS/ASCO) Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016).

h Vital signs (respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated position, and temperature) will be taken before and after study treatment administration.

i ECOG Performance Status should be assessed at least every 3 months during the neoadjuvant treatment period, prior to surgery, and at the treatment completion or discontinuation visit (if applicable).

j Screening measurements can be used as Day 1 assessments if performed within 3 days prior to Cycle 1.

k Weight will be measured during screening and on Day 1 of each cycle. If variation of ± 10% occurs, as compared with screening, the trastuzumab IV and chemotherapy doses will be recalculated.

l Screening tumor staging procedures are not mandatory and should be performed as per local practice, in alignment with national guidelines and as clinically indicated within 28 days of randomization.

m Provided that the participant's clinical status has not changed, the screening mammogram can be performed up to 42 days prior to the start of treatment. The mammogram at screening, pre-surgery, and treatment completion or discontinuation visit can be replaced by other conventional imaging methods such as MRI or ultrasound per local medical practice, at the investigator's discretion, but the same method of assessment must be used throughout for an individual participant. If another method is used, this must be performed within the 28-day screening window. *The timing between the pre-surgery mammogram and surgery should be as per local practice /guidance.* If a mammogram has been conducted as part of routine preventive care within 4 months of the treatment completion or discontinuation visit, it may be used in lieu of the end-of-study mammogram.

n Tumor response assessment will be performed at screening, prior to each new cycle of therapy, and at treatment discontinuation (if applicable), by clinical breast examination (mandatory) and other methods of evaluation as per routine clinical practice.

o If the participant has not had an LVEF measured in the last 12 weeks, an ECHO or MUGA should be performed at the *baseline* screening visit. For participants whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each participant and is preferably performed and assessed by the same assessor. *All LVEF assessments will be performed during Days 15–21 of 3-week cycles prior to the cycle indicated, LVEF assessment may also be performed on Day 1 of treatment. The results must be available before treatment is administered. Apart from the specified mandatory LVEF assessment, the investigator may request additional assessment based on the individual participant's cardiovascular function with a minimum frequency of 3–4 months.*

p Participants should not start HER2-targeted therapy if their LVEF is < 50% after anthracycline treatment. This ECHO/MUGA assessment should be performed prior to administration of any treatment at Cycle 5.

q Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. Albumin should be measured at Screening for determining participant eligibility. Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN. During the treatment period, bloods for hematology / biochemistry may be taken within three days prior to study treatment administration. *The assessment of hematology / limited biochemistry prior to surgery can be done as per local clinical practice; however, the results must be available prior to the surgery.*

r All female participants of childbearing potential (refer to Section 5.1.1 for definition) will have a serum pregnancy test performed at screening within 7 days prior to the first administration of study medication (with result available prior to dosing). Urine pregnancy tests should be repeated during the treatment period within 7 days prior to cycle 3 and at last cycle of neoadjuvant phase (and as clinically indicated), as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period urine pregnancy test results must be available prior to the drug infusion/injection. Pregnancy test at 7 months (i.e., between 6–9 months follow up) can be performed if indicated. Note that participants are required to continue contraception for 7 months after study treatment is complete.

s Completed before treatment is administered on Day 1 of the indicated treatment cycles.

t All participants in Arm A receive a pertuzumab loading dose of 840 mg IV and a trastuzumab loading dose of 8 mg/kg IV followed by the maintenance dose of pertuzumab 420 mg IV and of trastuzumab 6 mg/kg IV. Participants who have had ≥ 6 weeks since their last pertuzumab and trastuzumab treatment must receive a loading dose before continuing with maintenance doses for subsequent administrations.

u All participants in Arm B receive a PH FDC SC loading dose of 1200 mg pertuzumab and 600 mg trastuzumab followed by the maintenance dose of PH FDC SC with 600 mg of pertuzumab and 600 mg of trastuzumab. Participants who have had ≥ 6 weeks since their last PH FDC SC treatment must receive a loading dose before continuing with maintenance doses for subsequent administrations.

v Participants receive docetaxel 75 mg/m² and carboplatin AUC 5–6 (area under the plasma concentration-time curve) given every 3 weeks, for 6 cycles (Cycles 1–6).

w Pathologic response assessment to be performed using the resected specimen by the local pathologist on the basis of guidelines to be provided in a Pathology Manual.

x After informed consent has been obtained, but prior to initiation of study *treatment*, only serious adverse events caused by protocol-mandated intervention should be reported. After initiation of study *treatment*, all adverse events will be reported until 28 days after the last 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 *treatment* (see Appendix 2).

y All concomitant medications used by the participant from 7 days prior to initiation of study *treatment* until the End of Treatment Visit will be reported.

z Treatment discontinuation visits will optimally be scheduled for 28 (± 7 days) following the last dose of study medication. All patients will return to the study site for a safety follow-up visit 6–9 months after the last dose of study treatment (see Table 4 for details).

aa The timing between the pre-surgery ECG and surgery should be as per local practice /guidance.

Table 2 Schedule of Activities for Neoadjuvant Phase: Treatment Option 2

		Neoadjuvant treatment period – Treatment Option 2 AC q3w x 4 followed by a taxane plus HER2-targeted therapy									
		3-week cycles									
Cycle	Screening [a]	1	2	3	4	5	6	7	8	Surgery [b]	Treatment discontinuation [aa]
Day	–28 to –1	1	1	1	1	1	1	1	1	1	
Informed consent [c]	x										
Medical history and demographics	x										
Complete physical examination [d] [e]	x	x							x		x
Local HER2 and hormone receptor status (HER2, ER, PgR) [f]	x										
Limited physical examination [d] [g]			x	x	x	x	x	x			
Vital signs [d] [h]	x	x	x	x	x	x	x	x	x		x
ECOG Performance Status [d] [i]		x [j]				x				x (Prior surgery)	x
Height [d]	x										
Weight [d] [k]	x	x	x	x	x	x	x	x	x		x
Tumor staging [l]	x										
Bilateral mammogram (or another imaging method as per local practice) [m]	x									x (Prior surgery)	x
Clinical tumor assessment / breast examination [d] [n]	x	x	x	x	x	x	x	x	x		x
ECG (12-lead)	x				x					x *[ab]* (Prior surgery)	
LVEF (ECHO or MUGA) [o]	x					x [p]					x
Hematology / limited biochemistry [q]	x	x [j]	x	x	x	x	x	x	x	x (Prior surgery)	x
Pregnancy test [r]	x			x					x		x
HIV, HBV, and HCV serology	x										

		Neoadjuvant treatment period – Treatment Option 2 AC q3w x 4 followed by a taxane plus HER2-targeted therapy									
		3-week cycles									
Cycle	Screening [a]	1	2	3	4	5	6	7	8	Surgery [b]	Treatment discontinuation [aa]
Day	–28 to –1	1	1	1	1	1	1	1	1	1	
HCPQ-Drug Preparation Area (Questions 1a–1b) - Appendix 6						x	x	x	x		
HCPQ-Drug Preparation Area (Questions 2–4) - Appendix 6									x		
HCPQ-Administering Treatment (Questions 1a–1g) - Appendix 7						x	x	x	x		
HCPQ-Administering Treatment (Questions 2–11) - Appendix 7									x		
EORTC QLQ-C30 - Appendix 8 [s]		x							x		
Arm A – P+H IV [t] (q3w x 4)						x (Loading dose)	x	x	x		
Arm B – PH FDC SC [u] (q3w x 4)						x (Loading dose)	x	x	x		
Doxorubicin (q3w x 4) [v]		x	x	x	x						
Cyclophosphamide (q3w x 4) [v]		x	x	x	x						
Docetaxel (q3w x 4) [w]						x	x	x	x		
Paclitaxel (qw x 12) [w]						Weekly for 12 weeks					
pCR post-surgery										x [x]	
Adverse events [y]	x	All adverse events and serious adverse events									
Concomitant medication [z]	x	Continuous									

AC = doxorubicin plus cyclophosphamide; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; HBV = hepatitis B virus; HCV = hepatitis C virus; HCPQ = healthcare professional questionnaires; HIV = human immunodeficiency virus; IV = Intravenous; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition (scan); pCR = pathologic complete response; PgR = progesterone receptor; SAE = serious adverse event.

Note: Unless otherwise specified, assessments should be performed within three days of the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. For all protocol-mandated study visits, a time window of ± 3 days is allowed. If a protocol mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date. Unscheduled visits may be performed if clinically indicated. The following assessments should be performed at a minimum: concomitant medications, adverse events, and vital signs. Additional assessments may be performed as clinically indicated, per investigator discretion. Participants may change from P+H IV (Arm A) treatment to PH FDC SC (Arm B) treatment, in

exceptional circumstances and as per investigator discretion. As such, these participants will continue on the study with the planned neoadjuvant and adjuvant phase of the study. Participants requesting to change from PH FDC SC to P+H IV in the neoadjuvant phase will be discontinued from the study. As such, these participants will be treated as per standard of care.

If participants discontinue from study treatment early, they will be asked to return to the clinic for a treatment completion / treatment discontinuation visit 28 days (± 7 days) after the final dose of study drug (see Table 4 for additional details).

a Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within 28 or 7 days of randomization (as indicated) may be used; such tests do not need to be repeated for screening. Individuals who do not meet the criteria for participation in this study may qualify for one re screening opportunities (for a total of two screenings per individual) at the investigator's discretion, as described in Section 5.4. *Randomization and the Day 1, Cycle 1 visit should take place within 3 days of the screening visit.*

b The surgery cannot be performed ≤ 2 weeks from the last systemic neoadjuvant therapy and must be performed ≤ 6 weeks after the last systemic neoadjuvant therapy. If surgery is significantly delayed (>42 days since the last P+H IV or PH FDC SC administration), a maximum of two additional cycles of P+H IV or PH FDC SC (depending on the treatment arm (A or B) assigned to the participant at randomization), can be administered at the investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. See Appendix 18 for details of the assessments that should be conducted for participants who require additional cycles of P+H IV or PH FDC SC due to a delay with surgery. PH FDC SC cannot be initiated within ≤ 2 weeks of surgery but must be initiated ≤ 9 weeks from the last administration of systemic neoadjuvant therapy.

c Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

d Assessment may be done within 3 days prior to the treatment day.

e Complete physical examinations should include physical measurements (body weight in kilograms and height in centimeters) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions CRF.

f Results of previous HER2/hormone receptor status diagnoses can be used to determine eligibility if the sample was tested in the 90 days prior to enrollment. Reassessment of HER2/hormone receptor status is not mandatory in these cases but can be done as per local decision. Hormone receptor-positive participants are to be prescribed endocrine therapy according to the local guidelines after completion of pre-operative chemotherapy and surgery. Endocrine therapy will be obtained locally by the investigational sites or will be provided by the Sponsor as per country requirements.

g Limited physical examinations are symptom-directed and, in addition to the scheduled examinations indicated, may be conducted by a mobile HCP as clinically indicated. New or worsened clinically significant abnormalities observed post-screening should be recorded as AEs on the Adverse Event electronic form. After the End of Treatment, physical examinations should be conducted by treating physician in accordance with institutional practice or the American Cancer Society/American Society of Clinical Oncology Breast Cancer (ACS/ASCO) Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016).

h Vital signs (respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated position, and temperature) will be taken before and after study treatment administration.

i ECOG Performance Status should be assessed at least every 3 months during the neoadjuvant treatment period, prior to surgery, and at the treatment completion or discontinuation visit (if applicable).

j Screening measurements can be used as Day 1 assessments if performed within 3 days prior to Cycle 1.

k Weight will be measured during screening and on Day 1 of each cycle. If variation of ± 10% occurs, as compared with screening, the trastuzumab IV and chemotherapy doses will be recalculated.

l Screening tumor staging procedures are not mandatory and should be performed as per local practice, in alignment with national guidelines and as clinically indicated within 28 days of randomization.

m Provided that the participant's clinical status has not changed, the screening mammogram can be performed up to 42 days prior to the start of treatment. The mammogram at screening, pre-surgery, and treatment completion or discontinuation visit can be replaced by other conventional imaging methods such as MRI or ultrasound per local medical practice, at the investigator's discretion, but the same method of assessment must be used throughout for an individual participant. If another method is used, this must be performed within the 28-day screening window. *The timing between the pre-surgery mammogram and surgery should be as per local practice /guidance.* If a mammogram has been conducted as part of routine preventive care within 4 months of the treatment completion or discontinuation visit, it may be used in lieu of the end-of-study mammogram.

n *T*umor response assessment will be performed *at screening,* prior to each new cycle of therapy*, and at treatment discontinuation (if applicable),* by clinical breast examination (mandatory) and other methods of evaluation as per routine clinical practice.

o If the participant has not had an LVEF measured in the last 12 weeks, an ECHO or MUGA should be performed at the *baseline* screening visit. For participants whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each participant and is preferably performed and assessed by the same assessor. *All LVEF assessments will be performed during Days 15–21 of 3-week cycles prior to the cycle indicated, LVEF assessment may also be performed on Day 1 of treatment. The results must be available before treatment is administered. Apart from the specified mandatory LVEF assessment, the investigator may request additional assessment based on the individual participant's cardiovascular function with a minimum frequency of 3–4 months.*

p Participants should not start HER2-targeted therapy if their LVEF is < 50% after anthracycline treatment. This ECHO/MUGA assessment should be performed prior to administration of any treatment at Cycle 5.

q Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. Albumin should be measured at Screening for determining participant eligibility. Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN. During the treatment period, bloods for hematology / biochemistry may be taken within three days prior to study treatment administration. Hematology / limited biochemistry assessments should be conducted at a minimum of every 3 weeks and can be conducted more frequently as per local practice. *The assessment of hematology / limited biochemistry prior to surgery can be done as per local clinical practice; however, the results must be available prior to the surgery.*

r All female participants of childbearing potential (refer to Section 5.1.1 for definition) will have a serum pregnancy test performed at screening within 7 days prior to the first administration of study medication (with result available prior to dosing). Urine pregnancy tests should be repeated during the treatment period within 7 days prior to cycle 3 and at last cycle of neoadjuvant phase (and as clinically indicated), as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. Pregnancy test at 7 months (i.e., between 6–9 months follow up) can be performed if indicated. Note that participants are required to continue contraception for 7 months after study treatment is complete.

s Completed before treatment is administered on Day 1 of the indicated treatment cycles.

t All participants in Arm A receive a pertuzumab loading dose of 840 mg IV and a trastuzumab loading dose of 8 mg/kg IV followed by the maintenance dose of pertuzumab 420 mg IV and of trastuzumab 6 mg/kg IV. Participants who have had ≥ 6 weeks since their last

pertuzumab and trastuzumab treatment must receive a loading dose before continuing with maintenance doses for subsequent administrations.

u All participants in Arm B receive a PH FDC SC loading dose of 1200 mg pertuzumab and 600 mg trastuzumab followed by the maintenance dose of PH FDC SC with 600 mg of pertuzumab and 600 mg of trastuzumab. Participants who have had ≥ 6 weeks since their last PH FDC SC treatment must receive a loading dose before continuing with maintenance doses for subsequent administrations.

v Participants receive doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV given every 3 weeks, for four cycles (Cycles 1–4).

w Participants receive **either** docetaxel (75–100 mg/m²) given every 3 weeks, for four cycles (Cycles 5–8) or paclitaxel (80 mg/m²) every week for 12 weeks during Cycles 5–8). The starting dose of docetaxel is 75mg/m^2 IV in Cycle 5 given every 3 weeks. At the investigator's discretion, the dose may be escalated to 100 mg/m^2 IV for subsequent cycles (Cycles 6–8) provided no dose-limiting toxicity occurs.

x Pathologic response assessment to be performed using the resected specimen by the local pathologist on the basis of guidelines to be provided in a Pathology Manual.

y After informed consent has been obtained, but prior to initiation of study *treatment*, only serious adverse events caused by protocol-mandated intervention should be reported. After initiation of study *treatment*, all adverse events will be reported until 28 days after the last 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 *treatment* (see Appendix 2).

z All concomitant medications used by the participant from 7 days prior to initiation of study *treatment* until the End of Treatment Visit will be reported.

aa Treatment discontinuation visits will optimally be scheduled for 28 (± 7 days) following the last dose of study medication. All patients will return to the study site for a safety follow-up visit 6–9 months after the last dose of study treatment (see Table 4 for details).

ab The timing between the pre-surgery ECG and surgery should be as per local practice /guidance.

Table 3 Schedule of Activities for Neoadjuvant Phase: Treatment Option 3

		Neoadjuvant treatment period – Treatment Option 3 ddAC q2w x 4 followed by a taxane plus HER2-targeted therapy									
		2-weekly cycles				3-weekly cycles					
Cycle	Screening [a]	1	2	3	4	5	6	7	8	Surgery [b]	Treatment discontinuation [aa]
Day	–28 to –1	1	1	1	1	1	1	1	1	1	
Informed consent [c]	x										
Medical history and demographics	x										
Complete physical examination [d] [e]	x	x							x		x
Local HER2 and hormone receptor status (HER2, ER, PgR) [f]	x										
Limited physical examination [d] [g]			x	x	x	x	x	x			
Vital signs [d] [h]	x	x	x	x	x	x	x	x	x		x
ECOG Performance Status [d] [i]		x [j]				x				x (Prior surgery)	x
Height [d]	x										
Weight [d] [k]	x	x	x	x	x	x	x	x	x		x
Tumor staging [l]	x										
Bilateral mammogram (or another imaging method as per local practice) [m]	x									x (Prior surgery)	x
Clinical tumor assessment / breast examination [d] [n]	x	x	x	x	x	x	x	x	x		x
ECG (12-lead)	x				x					x *[ab]* (Prior surgery)	
LVEF (ECHO or MUGA) [o]	x					x [p]					x
Hematology / limited biochemistry [q]	x	x [j]	x	x	x	x	x	x	x	x (Prior surgery)	x
Pregnancy test [r]	x			x					x		x
HIV, HBV, and HCV serology	x										

		Neoadjuvant treatment period – Treatment Option 3 ddAC q2w x 4 followed by a taxane plus HER2-targeted therapy									
		2-weekly cycles				3-weekly cycles					
Cycle	Screening [a]	1	2	3	4	5	6	7	8	Surgery [b]	Treatment discontinuation [aa]
Day	–28 to –1	1	1	1	1	1	1	1	1	1	
HCPQ-Drug Preparation Area (Questions 1a–1b) - Appendix 6						x	x	x	x		
HCPQ-Drug Preparation Area (Questions 2–4) - Appendix 6									x		
HCPQ-Administering Treatment (Questions 1a–1g) - Appendix 7						x	x	x	x		
HCPQ-Administering Treatment (Questions 2–11) - Appendix 7									x		
EORTC QLQ-C30 - Appendix 8 [s]		x							x		
Arm A – P+H IV [t] (q3w x 4)						x (Loading dose)	x	x	x		
Arm B – PH FDC SC [u] (q3w x 4)						x (Loading dose)	x	x	x		
ddDoxorubicin (q2w x 4) [v]		x	x	x	x						
ddCyclophosphamide (q2w x 4) [v]		x	x	x	x						
Docetaxel (q3w x 4) [w]						x	x	x	x		
Paclitaxel (qw x 12) [w]						Weekly for 12 weeks					
pCR post-surgery										x [x]	
Adverse events [y]	x	All adverse events and serious adverse events									
Concomitant medication [z]	x	Continuous									

dd = dose-dense; AC = doxorubicin plus cyclophosphamide; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; HBV = hepatitis B virus; HCV = hepatitis C virus; HCPQ = healthcare professional questionnaires; HIV = human immunodeficiency virus; IV = Intravenous; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition (scan); pCR = pathologic complete response; PgR = progesterone receptor; SAE = serious adverse event.

Note: Unless otherwise specified, assessments should be performed within three days of the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. For all protocol-mandated study visits, a time window of ± 3 days is allowed. If a protocol mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date. Unscheduled visits may be performed if clinically indicated. The following assessments should be performed at a minimum: concomitant medications, adverse events, and vital signs. Additional assessments may be performed as clinically indicated, per investigator discretion. Participants may change from P+H IV (Arm A) treatment to PH FDC SC (Arm B) treatment, in

exceptional circumstances and as per investigator discretion. As such, these participants will continue on the study with the planned neoadjuvant and adjuvant phase of the study. Participants requesting to change from PH FDC SC to P+H IV in the neoadjuvant phase will be discontinued from the study. As such, these participants will be treated as per standard of care.

If participants discontinue from study treatment early, they will be asked to return to the clinic for a treatment completion / treatment discontinuation visit 28 days (± 7 days) after the final dose of study drug (see Table 4 for additional details).

a Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within 28 or 7 days of randomization (as indicated) may be used; such tests do not need to be repeated for screening. Individuals who do not meet the criteria for participation in this study may qualify for one re screening opportunities (for a total of two screenings per individual) at the investigator's discretion, as described in Section 5.4. *Randomization and the Day 1, Cycle 1 visit should take place within 3 days of the screening visit.*

b The surgery cannot be performed ≤ 2 weeks from the last systemic neoadjuvant therapy and must be performed ≤ 6 weeks of the last systemic neoadjuvant therapy. If surgery is significantly delayed (>42 days since the last P+H IV or PH FDC SC administration), a maximum of two additional cycles of P+H IV or PH FDC SC (depending on the treatment arm (A or B) assigned to the participant at randomization), can be administered at the investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. See Appendix 18 for details of the assessments that should be conducted for participants who require additional cycles of P+H IV or PH FDC SC due to a delay with surgery. PH FDC SC cannot be initiated within ≤ 2 weeks of surgery but must be initiated ≤ 9 weeks from the last administration of systemic neoadjuvant therapy.

c Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

d Assessment may be done within 3 days prior to the treatment day.

e Complete physical examinations should include physical measurements (body weight in kilograms and height in centimeters) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions CRF.

f Results of previous HER2/hormone receptor status diagnoses can be used to determine eligibility if the sample was tested in the 90 days prior to enrollment. Reassessment of HER2/hormone receptor status is not mandatory in these cases but can be done as per local decision. Hormone receptor-positive participants are to be prescribed endocrine therapy according to the local guidelines after completion of pre-operative chemotherapy and surgery. Endocrine therapy will be obtained locally by the investigational sites or will be provided by the Sponsor as per country requirements.

g Limited physical examinations are symptom-directed and, in addition to the scheduled examinations indicated, may be conducted by a mobile HCP as clinically indicated. New or worsened clinically significant abnormalities observed post-screening should be recorded as AEs on the Adverse Event electronic form. After the End of Treatment, physical examinations should be conducted by treating physician in accordance with institutional practice or the American Cancer Society/American Society of Clinical Oncology Breast Cancer (ACS/ASCO) Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016).

h Vital signs (respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated position, and temperature) will be taken before and after study treatment administration.

i ECOG Performance Status should be assessed at least every 3 months during the neoadjuvant treatment period, prior to surgery, and at the treatment completion or discontinuation visit (if applicable).

j Screening measurements can be used as Day 1 assessments if performed within 3 days prior to Cycle 1.

k Weight will be measured during screening and on Day 1 of each cycle. If variation of ± 10% occurs, as compared with screening, the trastuzumab IV and chemotherapy doses will be recalculated.

l Screening tumor staging procedures are not mandatory and should be performed as per local practice, in alignment with national guidelines and as clinically indicated within 28 days of randomization.

m Provided that the participant's clinical status has not changed, the screening mammogram can be performed up to 42 days prior to the start of treatment. The mammogram at screening, pre-surgery, and treatment completion or discontinuation visit can be replaced by other conventional imaging methods such as MRI or ultrasound per local medical practice, at the investigator's discretion, but the same method of assessment must be used throughout for an individual participant. If another method is used, this must be performed within the 28-day screening window. *The timing between the pre-surgery mammogram and surgery should be as per local practice /guidance.* If a mammogram has been conducted as part of routine preventive care within 4 months of the treatment completion or discontinuation visit, it may be used in lieu of the end-of-study mammogram.

n *T*umor response assessment will be performed *at screening,* prior to each new cycle of therapy*, and at treatment discontinuation (if applicable),* by clinical breast examination (mandatory) and other methods of evaluation as per routine clinical practice.

o If the participant has not had an LVEF measured in the last 12 weeks, an ECHO or MUGA should be performed at the *baseline* screening visit. For participants whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each participant and is preferably performed and assessed by the same assessor. *All LVEF assessments will be performed during Days 15–21 of 3-week cycles prior to the cycle indicated, LVEF assessment may also be performed on Day 1 of treatment. The results must be available before treatment is administered. Apart from the specified mandatory LVEF assessment, the investigator may request additional assessment based on the individual participant's cardiovascular function with a minimum frequency of 3–4 months.*

p Participants should not start HER2-targeted therapy if their LVEF is < 50% after anthracycline treatment. This ECHO/MUGA assessment should be performed prior to administration of any treatment at Cycle 5.

q Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. Albumin should be measured at Screening for determining participant eligibility. Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN. During the treatment period, bloods for hematology / biochemistry may be taken within three days prior to study treatment administration. Hematology / limited biochemistry assessments should be conducted at a minimum of every 3 weeks and can be conducted more frequently as per local practice. *The assessment of hematology / limited biochemistry prior to surgery can be done as per local clinical practice; however, the results must be available prior to the surgery.*

r All female participants of childbearing potential (refer to Section 5.1.1 for definition) will have a serum pregnancy test performed at screening within 7 days prior to the first administration of study medication (with result available prior to dosing). Urine pregnancy tests should be repeated during the treatment period within 7 days prior to cycle 3 and at last cycle of neoadjuvant phase (and as clinically indicated), as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. Pregnancy test at 7 months (i.e., between 6–9 months follow up) can be performed if indicated. Note that participants are required to continue contraception for 7 months after study treatment is complete.

s Completed before treatment is administered on Day 1 of the indicated treatment cycles.

t All participants in Arm A receive a pertuzumab loading dose of 840 mg IV and a trastuzumab loading dose of 8 mg/kg IV followed by the maintenance dose of pertuzumab 420 mg IV and of trastuzumab 6 mg/kg IV. Participants who have had ≥ 6 weeks since their last

pertuzumab and trastuzumab treatment must receive a loading dose before continuing with maintenance doses for subsequent administrations.

u All participants in Arm B receive a PH FDC SC loading dose of 1200 mg pertuzumab and 600 mg trastuzumab followed by the maintenance dose of PH FDC SC with 600 mg of pertuzumab and 600 mg of trastuzumab. Participants who have had ≥ 6 weeks since their last PH FDC SC treatment must receive a loading dose before continuing with maintenance doses for subsequent administrations.

v Participants receive dose-dense doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV given every 2 weeks, for four cycles (Cycles 1–4).

w *The time period between Cycle 4 and Cycle 5 can be either 2 or 3 weeks, as per local practice or investigator discretion.* Participants receive **either** docetaxel 75–100 mg/m² given every 3 weeks, for four cycles (Cycles 5–8) or paclitaxel 80 mg/m² (every week for 12 weeks during Cycles 5–8). The starting dose of docetaxel is 75mg/m^2 IV in Cycle 5 given every 3 weeks. At the investigator's discretion, the dose may be escalated to 100 mg/m^2 IV for subsequent cycles (Cycles 6–8) provided no dose-limiting toxicity occurs.

x Pathologic response assessment to be performed using the resected specimen by the local pathologist on the basis of guidelines to be provided in a Pathology Manual.

y After informed consent has been obtained, but prior to initiation of study *treatment*, only serious adverse events caused by protocol-mandated intervention should be reported. After initiation of study *treatment*, all adverse events will be reported until 28 days after the last 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 *treatment* (see Appendix 2).

z All concomitant medications used by the participant from 7 days prior to initiation of study *treatment* until the End of Treatment Visit will be reported.

aa Treatment discontinuation visits will optimally be scheduled for 28 (± 7 days) following the last dose of study medication. All patients will return to the study site for a safety follow-up visit 6–9 months after the last dose of study treatment (see Table 4 for details).

ab The timing between the pre-surgery ECG and surgery should be as per local practice /guidance.

Table 4 Schedule of Activities: *Adjuvant treatment period – PH FDC SC (Arms C and D)*

	Adjuvant Treatment Period											F/U (6–9 months post last dose)
	Run-in period [a]		Cross-over Period						Treatment continuation period		Treatment Completion / disc. [c]	
Cycle	**1 (Baseline status)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Until a total of 18 cycles [b]**		
Day	1	1	1	1	1	1	1	1	1	1	-	
Complete physical examination [d] [e]										x [f] (Last cycle)	x	
Limited physical examination [d] [g]	x	x	x	x	x	x	x	x	x	x (Except for last cycle)		
Vital signs [d] [h]	x	x	x	x	x	x	x	x	x	x	x	
ECOG performance status [d] [i]	x		x			x			x	x (Last cycle)	x	
Weight [d]	x	x	x	x	x	x	x	x	x	x	x	
Clinical breast examination [d] [*j*]	x				x (Arm C)	x (Arm D)			x [f]	x [f] (Last cycle)	x	
Bilateral mammogram (or another imaging method as, per local practice) [*k*]											x	
LVEF (ECHO or MUGA) [*l*]	x				x (Arm C)	x (Arm D)			x [f]	x [f] (Last cycle)	x	
Pregnancy test [*m*]	x				x (Arm C)	x (Arm D)			x [f]	x [f] (Last cycle)	x	x
Hematology / limited biochemistry [*n*]	x				x (Arm C)	x (Arm D)			x *[f]*	x [f] (Last cycle)	x	
General health status (site staff) [*o*]			x (Arm D)	x (Arm D)	x (Arm D)	x (Arm C)	x (Arm C)	x (Arm C)	x	x		
Health status (mobile HCP) [*p*]			x (Arm D)	x (Arm D)	x (Arm D)	x (Arm C)	x (Arm C)	x (Arm C)	x	x		
Arm C: PH FDC SC (q3w) [*q*]	x (At hospital)	x (At hospital)	x (At hospital)	x (At hospital)	x (At hospital)	x (At home)	x (At home)	x (At home)	x [*r*]	x [*r*]		
Arm D: PH FDC SC (q3w) [*q*]	x (At hospital)	x (At hospital)	x (At home)	x (At home)	x (At home)	x (At hospital)	x (At hospital)	x (At hospital)	x [*r*]	x [*r*]		

	Adjuvant Treatment Period											F/U (6–9 months post last dose)
	Run-in period [a]		Cross-over Period						Treatment continuation period		Treatment Completion / disc. [c]	
Cycle	**1 (Baseline status)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Until a total of 18 cycles [b]**		
Day	1	1	1	1	1	1	1	1	1	1	-	
PPQ – Appendix 5								x [s]				
HCPQ-Drug Preparation Area Questions 1a–1c – Appendix 9					x			x				
HCPQ-Drug Preparation Area Questions 2–4 – Appendix 9								x				
HCPQ-Administering Treatment Questions 1a–1i – Appendix 10					x			x				
HCPQ-Administering Treatment Questions 1j–1l & 2–7 – Appendix 10								x				
EORTC QLQ-C30 [t] – Appendix 8	x		x		x			x		x (Last cycle)		
The participant selects the setting for further treatment								x [u]				
Adverse events [v]	All adverse events and serious adverse events											x
Concomitant medication [w]	Continuous											

ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; F/U = follow-up; *HCPQ = healthcare professional questionnaires; IV = Intravenous;* LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition (scan); PPQ = patient preference questionnaire.

Note: Unless otherwise specified, assessments should be performed within three days of the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. For all protocol-mandated study visits, a time window of ± 3 days is allowed. If a protocol mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date. Unscheduled visits may be performed if clinically indicated. The following assessments should be performed at a minimum: concomitant medications, adverse events, and vital signs. Additional assessments may be performed as clinically indicated, per investigator discretion. The assessments at Cycles 6, 7, and 8 of Arm C, Cycles 3, 4, and 5 of Arm D, and Cycle 9 onwards for both arms (if the participant has selected home administration for the remaining treatment cycles) will be performed by the mobile healthcare professional, unless otherwise indicated. The mobile healthcare professional will contact the participant within 3 working days before the visit to confirm the time and place of the visit.

a In the event of delays/ interruptions of radiotherapy, PH FDC SC can be provided for one additional cycle during the run-in period (maximum 3 cycles of PH FDC SC during run-in) and the assessments listed for Cycle 2 should be repeated for this additional cycle. At the next treatment cycle, the sites should follow the assessments listed for the first cycle of the cross-over period *(cycle 3 in Table 4*).

b Treatment will be given so that in total, 18 cycles of HER2-directed therapy (P+H IV or PH FDC SC) are administered, inclusive of therapy given both in the neoadjuvant and adjuvant setting unless disease recurrence (per institutional practice or according *to* the *American Cancer Society/American Society of Clinical Oncology Breast Cancer (*ACS/ASCO*)* Breast Cancer Survivorship Care Guideline; Runowicz et al. 2016; see Section 8.2.7), unacceptable toxicity, or participant withdrawal.

c Treatment completion or discontinuation visits will optimally be scheduled for 28 (± 7 days) following the last dose of study medication and will include all evaluations scheduled for the final visit.

d Assessment may be done within 3 days prior to the treatment day.

e Complete physical examinations should include physical measurements (body weight in kilograms and height in centimeters) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. After the End of Treatment, physical examinations should be conducted by treating physician in accordance with institutional practice or the ACS/ASCO Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016).

f Assessment may be done within 3 days prior to treatment day (within the hospital) for participants who selected *to be treated at home during the treatment continuation period*.

g Limited physical examinations are symptom-directed and, in addition to the scheduled examinations indicated, may be conducted by a mobile HCP as clinically indicated *and in accordance with institutional practice or the ACS/ASCO Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016)*. New or worsened clinically significant abnormalities observed post-baseline should be recorded as AEs on the Adverse Event electronic form.

h Vital signs (respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated position, and temperature) will be taken before and after study treatment administration. Additional vital sign measurement will be done after administering anaphylactic medication if the participant experiences hypersensitivity or other administration-related reactions during administration of PH FDC SC (see Section 8.2.2).

i ECOG Performance Status should be assessed by the HCP at least every 3–4 months during the adjuvant treatment period and at the treatment completion or discontinuation visit.

j During the adjuvant treatment period, clinical breast examination should be performed to detect signs of locoregional relapse at least every 3–4 months (Cycle 1, Cycle 5 or 6, Cycle 9, and last cycle) and at the treatment completion or discontinuation visit.

k The mammogram at treatment completion or discontinuation visit can be replaced by other conventional imaging methods such as MRI or ultrasound as per local medical practice, at the investigator's discretion, but the same method of assessment must be used throughout for an individual participant. If a mammogram has been conducted as part of routine preventive care within 4 months of the treatment completion or discontinuation visit, it may be used in lieu of the end of study mammogram.

l For participants whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each participant and is preferably performed and assessed by the same assessor. *All LVEF assessments will be performed during Days 15–21 of 3-week cycles prior to the cycle indicated, LVEF assessment may also be performed on Day 1 of treatment. Results of LVEF assessments must be available before treatment is administered and according to the scheduled timepoints. Apart from the specified mandatory LVEF assessment, the investigator may request additional assessment based on the individual participant's cardiovascular function with a minimum frequency of 3–4 months.*

m All female participants of childbearing potential (refer to Section 5.1.1 for definition) will have a urine pregnancy test (as clinically indicated) at cycle 1, 5 or 6, 9, and last cycle during adjuvant phase; as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. Pregnancy test at 7 months (i.e., between 6–9 months follow-up) can be performed if indicated. Note that participants are required to continue contraception for 7 months after study treatment is complete.

n Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. Albumin should be measured at Screening for determining participant eligibility. Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN. During the treatment period, bloods for hematology / biochemistry may be taken within three days prior to study treatment administration.

o The general health status check, via phone call, by the treating physician/ site study nurse can be done up to 5 days prior to home treatment visit. The treating physician will provide authorization for the home visit.

p During home visits, the mobile healthcare professional will complete the study assessments as requested by the study site (in line with the schedule of activities). The mobile healthcare professional will provide the information collected to the treating physician (via phone call), who will determine if the participant should receive the next PH FDC SC treatment. If required, the study investigator may request the participant attends the hospital for assessment by the treating physician.

q All participants receive maintenance dose of 600 mg pertuzumab and 600 mg trastuzumab. Participants who have had ≥ 6 weeks since their last pertuzumab and trastuzumab/PH FDC SC treatment must receive a loading dose before continuing with maintenance doses for subsequent administrations.

r After the cross-over treatment period, participants will receive the remaining PH FDC SC treatment cycles required, to complete the planned 18 cycles unless disease recurrence, unacceptable toxicity, or participant withdrawal. Study treatment during this treatment continuation period will be administered either in the hospital or in the home setting, as selected by the participant at the end of the cross-over period.

s The Patient Preference Questionnaire (PPQ) must be completed once the participant has completed the cross-over period of adjuvant treatment (i.e., following study treatment administration on Day 1, Cycle 8, or Day 1, Cycle 9, if an additional cycle of PH FDC SC was administered due to delays/ interruptions of radiotherapy [see Section 4.1.2]). Participants who discontinued study treatment prior to the last cycle of the cross-over period should complete the questionnaire at the time of discontinuation as long as they have received at least one dose PH FDC SC in the home setting.

t Completed before treatment is administered on Day 1 of the indicated treatment cycles.

u Immediately after the PPQ has been completed (i.e., once the participant has completed the cross-over period), the participant will choose whether to receive the remaining cycles of PH FDC SC in the home or hospital setting (to complete a total of 18 cycles of treatment with pertuzumab and trastuzumab in the (neo)adjuvant setting). Participants can request to change from home administration to hospital administration (and vice-versa) during the treatment continuation period, but not during the treatment cross-over period. This change can occur once only.

v After informed consent has been obtained, but prior to initiation of study $treatment$, only serious adverse events caused by protocol-mandated intervention should be reported. After initiation of study $treatment$, all adverse events will be reported until 28 days after the last 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 $treatment$ (see Appendix 2).

w All concomitant medications used by the participant from 7 days prior to initiation of study $treatment$ until the End of Treatment Visit will be reported.

Table 5 Schedule of Activities: Adjuvant treatment period – Trastuzumab emtansine IV (Arm E)

	Adjuvant Treatment Period											F/U (6–9 months post last dose)
Cycle	1 (Baseline status) [a]	2	3	4	5	6	7	8	9	Until a total of 14 cycles [b]	Treatment Completion/ disc. [c]	
Day	1	1	1	1	1	1	1	1	1	1	-	
Complete physical examination [d] [e]										x (Last cycle)	x	
Limited physical examination [d] [f]	x	x	x	x	x	x	x	x	x	x (Except for last cycle)		
Vital signs [d] [g]	x	x	x	x	x	x	x	x	x	x	x	
ECOG performance status [d] [h]	x		x			x			x	x (Last cycle)	x	
Weight [d] [i]	x	x	x	x	x	x	x	x	x	x	x	
Clinical breast examination [d] [j]	x				x				x	x (Last cycle)	x	
Bilateral mammogram (or another imaging method as, per local practice) [k]											x	
LVEF (ECHO or MUGA) [l]	x				x				x	x (Last cycle)	x	
Pregnancy test [m]	x				x				x	x (Last cycle)	x	x
Hematology / limited biochemistry [n]	x	x	x	x	x [o]	x [o]	x [o]	x [o]	x [o]	x [o] (Until completion of 14 cycles)	x [o]	
Trastuzumab emtansine IV (q3w)	x	x	x	x	x	x	x	x	x	x (until 14 cycles)		
EORTC QLQ-C30 [p] – Appendix 8	x						x			x (Cycle 14)		
Adverse events [q]	All adverse events and serious adverse events											x
Concomitant medication [r]	Continuous											

ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; F/U = follow-up; IV = Intravenous; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition (scan).

Note: Unless otherwise specified, assessments should be performed within three days of the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. For all protocol-mandated study visits, a time window of ± 3 days is allowed. If a protocol mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date. Unscheduled visits may be performed if clinically indicated. The following assessments should be performed at a minimum: concomitant medications, adverse events, and vital signs. Additional assessments may be performed as clinically indicated, per investigator discretion.

a Radiotherapy should be given as clinically indicated and the timing to start the radiotherapy should be based on the local practices, but it must start within 6 weeks after surgery.

b For a total of 14 cycles. See Section 4.1.2 for guidance on how to treat participants who develop an intolerance to trastuzumab emtansine. Trastuzumab emtansine cannot be initiated if the platelet count is <100,000/mL at Cycle 1. Trastuzumab emtansine has not been studied in patients with platelet counts <100,000/mL prior to initiation of treatment.

c Treatment completion or discontinuation visits will optimally be scheduled for 28 (± 7 days) following the last dose of study medication and will include all evaluations scheduled for the final visit.

d Assessment may be done within 3 days prior to the treatment day.

e Complete physical examinations should include physical measurements (body weight in kilograms and height in centimeters) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. After the End of Treatment, physical examinations should be conducted by treating physician in accordance with institutional practice or the ACS/ASCO Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016).

f Limited physical examinations are symptom-directed and, in addition to the scheduled examinations indicated, may be conducted by the treating physician in accordance with institutional practice or the ACS/ASCO Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016). New or worsened clinically significant abnormalities observed post-baseline should be recorded as AEs on the Adverse Event electronic form.

g Vital signs (respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated position, and temperature) will be taken before and after study treatment administration. Additional vital sign measurement will be done after administering anaphylactic medication if the participant experiences hypersensitivity or other administration-related reactions during administration of trastuzumab emtansine (see Section 8.2.2).

h ECOG Performance Status should be assessed by the HCP at least every 3–4 months during the adjuvant treatment period and at the treatment completion or discontinuation visit.

i Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with the baseline weight after surgery to determine if the dose of trastuzumab emtansine should be adjusted.

j During the adjuvant treatment period, clinical breast examination should be performed to detect signs of locoregional relapse at least every 3–4 months (Cycle 1, Cycle 5 or 6, Cycle 9, and last cycle) and at the treatment completion or discontinuation visit.

k The mammogram at treatment completion or discontinuation visit can be replaced by other conventional imaging methods such as MRI or ultrasound as per local medical practice, at the investigator's discretion, but the same method of assessment must be used throughout for an individual participant. If a mammogram has been conducted as part of routine preventive care within 4 months of the treatment completion or discontinuation visit, it may be used in lieu of the end of study mammogram.

l *For participants whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each participant and is preferably performed and assessed by the same assessor. All LVEF assessments will be performed during Days 15–21 of 3-week cycles prior to the cycle indicated, LVEF assessment may also be performed on Day 1 of treatment. Results of LVEF assessments must be available before treatment is administered and according to the scheduled timepoints. Apart from the specified mandatory LVEF assessment, the investigator may request additional assessment based on the individual participant's cardiovascular function with a minimum frequency of 3–4 months.*

m *All female participants of childbearing potential (refer to Section 5.1.1 for definition) will have a urine pregnancy test (as clinically indicated) at cycle 1, 5 or 6, 9, and last cycle during adjuvant phase; as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. Pregnancy test at 7 months (i.e., between 6–9 months follow-up) can be performed if indicated. Note that participants are required to continue contraception for 7 months after study treatment is complete.*

n *Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. Albumin should be measured at Screening for determining participant eligibility. Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN. During the treatment period, bloods for hematology / biochemistry may be taken within three days prior to study treatment administration.*

o *After the first 4 cycles, if there are no Grade 3/4 toxicities, hematology tests should be done at every subsequent cycle, and biochemistry tests should be done every 3 cycles, i.e., Cycle 7, Cycle 10, Cycle 13.*

p *Completed before treatment is administered on Day 1 of the indicated treatment cycles.*

q *After informed consent has been obtained, but prior to initiation of study treatment, only serious adverse events caused by protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 28 days after the last 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 treatment (see Appendix 2).*

r *All concomitant medications used by the participant from 7 days prior to initiation of study treatment until the End of Treatment Visit will be reported.*

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to evaluate the patient-reported preference for the pertuzumab and trastuzumab (PH) fixed-dose combination (FDC) for subcutaneous (SC) administration (PH FDC SC) in the home setting compared with the hospital setting in participants with early or locally advanced/inflammatory human epidermal growth factor receptor 2-positive (HER2+) breast cancer.

Moreover, safety and tolerability of SC versus IV administration of pertuzumab and trastuzumab will be assessed using the following treatment:

- Pertuzumab and trastuzumab administered by IV infusion in the hospital (P+H IV)
- Fixed-dose combination of pertuzumab and trastuzumab administered by SC injections in the hospital and the home setting (PH FDC SC).

The in-hospital setting may include any care level with Oncology services other than primary care level facilities, either private or public.

The administration of PH FDC SC in the home setting during the adjuvant phase in this study will be conducted by healthcare professionals (HCPs) provided by a mobile HCP vendor. In exceptional circumstances, as approved by the Sponsor, HCPs from study sites may undertake the home health visits.

The SC delivery of biotherapeutics is well-established as a route of administration that is effective and well-tolerated across many therapeutic areas (Collins et al. 2020). It can offer several advantages over IV administration, including the convenience of self-administration, improved patient experience, reduced treatment burden and lower healthcare costs.

Moreover, the reduction in hospital time of the patient will reduce the patient's exposure to nosocomial pathogens and reduce the burden on healthcare systems.

Clinical data from Studies BO30185, WO40324 (FeDeriCa), and MO40628 (PHranceSCa) showed that PH FDC SC is well tolerated, with the safety profile generally consistent with the safety profile of pertuzumab and trastuzumab IV, except for adverse events associated with subcutaneous route of administration. No new safety signals were identified from these studies. The safety of PH FDC SC administered at home by nurse providers in patients receiving maintenance HER2-targeted therapy is being investigated in a U.S. Expanded Access Program (Study AL42478). Study MO43110 will provide insights on patient's preference for home administration of PH FDC SC, for which data are limited. In addition, study MO43110 will collect safety and tolerability data for PH FDC SC administered in the home setting and hospital setting during the cross-over period and the entire adjuvant treatment period, to generate further information on the safety and tolerability of PH FDC SC.

2.2 BACKGROUND

According to the Global Cancer Observatory, breast cancer is number one in incidence and mortality compared to all cancers (Ferlay et al. 2020). Approximately 20% of breast cancers strongly overexpress HER2 (Artega et al. 2011). This is usually the result of amplification of the gene encoding HER2, which is found on chromosome 17 (Wolff et al. 2018). HER2 belongs to the family of human epidermal growth factor receptors (HER) (which also includes HER1 [also known as epidermal growth factor receptor (EGFR)], HER3, and HER4) that mediate normal cell growth, survival, and differentiation.

Primary breast cancers with HER2 amplification and overexpression were found to have a poor prognosis, including a greater risk of relapse and shortened survival, compared with tumors without this abnormality (Slamon et al. 1987; Toikkanen et al. 1992; Andrulis et al. 1998; Pauletti et al. 2000; Rubin and Yarden 2001).

The combination of pertuzumab and trastuzumab with chemotherapy has become the standard of care for treating HER2+ early and metastatic breast cancer (Gradisher et al. 2021).

PH FDC SC is a ready-to-use formulation of pertuzumab and trastuzumab co-formulated with recombinant human PH20 hyaluronidase (rHuPH20) developed to improve dispersion of large volumes of drugs when administered subcutaneously (i.e., it functions as a permeation enhancer). PH FDC SC was approved by the U.S. Food and Drug Administration (FDA) on 29th June 2020 (FDA 2020a; FDA 2020b), *by* the European Medicines Agency (EMA) on 21st December 2020 (EMA 2020), *and in numerous other major countries worldwide*.

PH FDC SC is indicated in combination with chemotherapy to treat patients with HER2+ early breast cancer and in combination with docetaxel in adult patients with HER2+ metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Detailed information on PH FDC SC is provided in the PH FDC SC Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to evaluate the patient-reported preference for PH FDC SC in the home setting compared with the hospital setting in participants with early or locally advanced/inflammatory HER2+ breast cancer.

The marketing approvals for PH FDC SC were based on results from the pivotal phase III FeDeriCa study (WO40324; Tan et al. 2021); this study assessed the pharmacokinetics, effectiveness, and safety of PH FDC SC in the hospital vs P+H IV among participants with HER2+ early breast cancer in the neoadjuvant–adjuvant setting.

The primary endpoint of the FeDeriCa study was non-inferiority of the cycle 7 pertuzumab serum trough concentration (C_{trough}; i.e., cycle 8 pre-dose pertuzumab concentration) within PH FDC SC versus P+H IV in the per-protocol pharmacokinetic population.

The primary endpoint of this study was met; the pertuzumab cycle 7 trough concentration within PH FDC SC (88.7 µg/mL) showed non-inferiority to that of pertuzumab (72.4 µg/mL), with a geometric mean ratio of 1.22 (90% confidence interval [CI] = 1.14–1.31). Moreover, the overall safety, including cardiac safety, was comparable between arms. The most common adverse events in both arms were alopecia, nausea, diarrhea, and anemia.

A phase II randomized, multicenter, open-label cross-over study was conducted to evaluate patient preference and satisfaction of SC administration of the PH FDC SC in the hospital in participants with HER2+ early breast cancer (MO40628; O'Shaughnessy et al. 2020). The primary analysis of study MO40628 (PHranceSCa) showed that 85% (136/160) of people receiving treatment for HER2+ breast cancer preferred SC treatment to IV administration due to less time in the clinic and more comfortable treatment administration (O'Shaughnessy et al. 2020; O'Shaughnessy et al. 2021).

The SC delivery of biotherapeutics is well-established as a route of administration that is effective and well-tolerated across many therapeutic areas (Collins et al. 2020). It can offer several advantages over IV administration, including the convenience of self-administration, improved patient experience, reduced treatment burden and lower healthcare costs.

There have been successful examples of drugs initially approved for IV administration that can now be safely administered as an SC injection in the out-of-hospital setting by HCPs (Denys et al. 2020; Wolfromm et al. 2017; Walsh et al. 2007). The out-of-hospital administration improves the patient quality of life and is more convenient, particularly for patients who live far from a hospital or have difficulty travelling. An ongoing Expanded Access Program in the U.S. is investigating PH FDC SC administration in the home setting (Study AL42478).

Refer to Appendix 3 for information on anticipated risks for PH FDC SC, P+H IV, and trastuzumab emtansine, and risk mitigation measures, including guidelines for managing adverse events associated with PH FDC SC, P+H IV, or trastuzumab emtansine.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PH FDC SC, as well as the other study treatments (P+H IV and trastuzumab emtansine) may be found in the PH FDC SC, pertuzumab, and trastuzumab emtansine Investigator's Brochures, and trastuzumab Summary of Product Characteristics (SmPC).

Considering the efficacy data in patients with early or locally advanced/inflammatory HER2+ breast cancer, the safety profile for PH FDC SC, and the risk mitigation measures for the study, the benefit–risk ratio is expected to be acceptable for the administration of PH FDC SC in the home setting.

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the patient-reported preference of PH FDC SC administration in the home setting compared with the hospital setting during the cross-over period of adjuvant treatment in participants with early or locally advanced/inflammatory HER2+ breast cancer.

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

In this protocol, "study treatment" refers to the combination of treatments assigned to participants as part of this study (i.e., fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration [PH FDC SC], alone or with chemotherapy; pertuzumab and trastuzumab IV [P+H IV] plus chemotherapy; and trastuzumab emtansine).

Table 6 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate patient preference of PH FDC SC administration in the home setting during the cross-over period of the adjuvant phase of the study	• Proportion of participants who preferred the administration of PH FDC SC in the home setting compared with the hospital setting in Question 1 of Patient Preference Questionnaire (PPQ) (Appendix 5)
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the perception of HCPs of time/resource use and convenience of PH FDC SC compared to P+H IV during the neoadjuvant phase of the study	• Responses of HCPs to the Healthcare Professional Questionnaire (HCPQ) by individual questions in the neoadjuvant phase (Appendix 6 and Appendix 7)
• Collect pathologic complete response (pCR) data post-surgery	• Proportion of participants achieving pCR, defined as eradication of invasive disease in the breast and axilla (i.e., ypT0/Tis ypN0), according to local pathologist assessment following the AJCC criteria (FDA 2020)
• To evaluate Health-related Quality of Life (HRQoL) during the neoadjuvant phase of the study	• HRQoL assessed by EORTC QLQ-C30 scores in the neoadjuvant phase (Appendix 8)
• To evaluate HRQoL with PH FDC SC administered during the adjuvant phase of the study	• HRQoL assessed by EORTC QLQ-C30 scores in the participants treated with PH FDC SC during the adjuvant phase (Appendix 8)

• To evaluate the perception of HCPs of time/resource use of PH FDC SC during the adjuvant cross-over period	• Responses of HCPs to the HCPQ by individual questions in the adjuvant cross-over period (Appendix 9 and Appendix 10)
• To evaluate HRQoL for participants treated with trastuzumab emtansine IV during the adjuvant phase	• HRQoL assessed by EORTC QLQ-C30 scores in the participants treated with trastuzumab emtansine IV during the adjuvant phase (Appendix 8)
• *To evaluate patient's choice of setting for the treatment continuation period*	• *Proportion of participants who selected the administration of PH FDC SC in the home setting compared with the hospital setting in the treatment continuation period*
Secondary Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of PH FDC SC and P+H IV during the neoadjuvant phase of the study	• Incidence, nature and severity of all AEs, Grade ≥ 3 AEs, SAEs, and cardiac AEs (including LVEF events) with severity determined according to National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) v5.0 (Appendix 14 and Appendix 16) • Incidence of premature withdrawal from the neoadjuvant treatment with PH FDC SC and P+H IV • Targeted vital signs and physical findings • Targeted clinical laboratory test results
• To evaluate the safety and tolerability of PH FDC SC administered in the home setting and hospital setting during the cross-over period and the entire adjuvant treatment period	• Incidence, nature, and severity of all AEs, Grade ≥ 3 AEs, SAEs, and cardiac AEs (including LVEF events) with severity determined according to NCI CTCAE v5.0 (Appendix 14 and Appendix 16) • Incidence of premature withdrawal from the adjuvant treatment with PH FDC SC • Targeted vital signs and physical findings • Targeted clinical laboratory test results
• To evaluate the safety and tolerability of trastuzumab emtansine IV during the adjuvant phase of the study	• Incidence, nature, and severity of all AEs, Grade ≥ 3 AEs, SAEs, and cardiac AEs (including LVEF events) with severity determined according to NCI CTCAE v5.0 (Appendix 14 and Appendix 16) • Incidence of premature withdrawal from the treatment with trastuzumab emtansine IV • Targeted vital signs and physical findings • Targeted clinical laboratory test results

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HCP = healthcare professional; HCPQ = Healthcare Professional Questionnaire; IV = intravenous; LVEF = Left ventricular ejection fraction; NCI = National Cancer Institute; pCR = pathologic complete response; PPQ = Patient Preference Questionnaire; SAE = serious adverse event.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a phase IIIb, multinational, multicenter, randomized, open-label study to evaluate the patient preference of PH FDC SC administration in the home setting compared with the hospital setting during the cross-over period of adjuvant treatment in participants with early or locally advanced/inflammatory HER2+ breast cancer.

The hospital setting for treatment administration may include any care level with Oncology services, other than primary care level facilities, either private or public.

The study will enroll participants with early or locally advanced/inflammatory HER2+ breast cancer consistent with the indication for treatment with neoadjuvant P+H IV plus chemotherapy or PH FDC SC plus chemotherapy in routine clinical practice and as recommended in local guidelines. Eligibility will be assessed within a 28-day screening period.

This study will consist of two phases.

4.1.1 Treatment During the Neoadjuvant Phase

During the neoadjuvant phase, the enrolled participants will be randomized in a ratio of 1:2, in one of the following treatment arms:

- **Arm A:** P+H IV every 3 weeks (q3w) plus chemotherapy (standard regimen) in the hospital.
- **Arm B:** PH FDC SC q3w plus chemotherapy (standard regimen) in the hospital.

In both arms, the investigator can select from one of three neoadjuvant chemotherapy options:

- **Option 1:** Docetaxel (75 mg/m²) and carboplatin (AUC 5–6 [area under the plasma concentration-time curve]) q3w for 6 cycles plus HER2-targeted therapy (Table 1)
- **Option 2:** Doxorubicin (60 mg/m²) plus cyclophosphamide (600 mg/m²) q3w for 4 cycles, followed by a taxane (docetaxel [75–100 mg/m²] q3w for 4 cycles or paclitaxel [80 mg/m²] every week for 12 cycles) plus HER2-targeted therapy (Table 2)
- **Option 3:** Dose-dense doxorubicin (60 mg/m²) plus cyclophosphamide (600 mg/m²) q2w for 4 cycles, followed by a taxane (docetaxel [75–100 mg/m²] q3w for 4 cycles or paclitaxel [80 mg/m²] every week for 12 cycles) plus HER2-targeted therapy (Table 3)

Randomization will be stratified by disease stage at screening (operable, locally advanced, or inflammatory, as defined in Section 6.3.1) and neoadjuvant chemotherapy option (anthracycline-free or anthracycline-based, as defined in Section 6.3.1).

Participants may change from P+H IV (Arm A) treatment to PH FDC SC (Arm B) treatment, in exceptional circumstances and as per investigator discretion. As such, these participants will continue on the study with the planned neoadjuvant and adjuvant phase of the study. Participants requesting to change from PH FDC SC to P+H IV in the neoadjuvant phase will be discontinued from the study. As such, these participants will be treated as per standard of care.

After completing their neoadjuvant therapy, participants from both arms will undergo surgical resection for early or locally advanced HER2+ breast cancer (if eligible for surgery; see Section 6.8.1). Surgery will be performed no earlier than 2 weeks after the last systemic neoadjuvant therapy and must be performed ≤ 6 weeks of the last systemic neoadjuvant therapy.

If surgery is significantly delayed (>42 days since the last P+H IV or PH FDC SC administration), a maximum of two additional cycles of P+H IV or PH FDC SC (depending on the treatment arm (A or B) assigned to the participant at randomization), can be administered at the investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. See Appendix 18 for details of the assessments that should be conducted for participants who require additional cycles of P+H IV or PH FDC SC due to a delay with surgery.

Local pathologists interpreting surgical specimens will determine if pCR has been achieved. pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis ypN0), according to the current American Joint Committee on Cancer (AJCC) staging system classification (FDA 2020).

Participants ineligible for surgery will be managed as per local practice and be withdrawn from study treatment. They will remain on study for follow-up of secondary and exploratory endpoints unless they have withdrawn consent from study participation.

4.1.2 Treatment During the Adjuvant Phase

4.1.2.1 *Participants Who Have Achieved pCR After Surgery*

Participants who have achieved pCR after surgery will first be treated with 2 cycles of PH FDC SC in the hospital (run-in period). *The study treatment PH FDC SC cannot be initiated within ≤ 2 weeks of surgery but must be initiated ≤ 9 weeks from the last administration of systemic neoadjuvant therapy.* If the interval between the administration of the first dose of PH FDC SC in the adjuvant phase and the administration of the last dose of PH FDC SC or P+H IV in the neoadjuvant phase is ≥ 6 weeks, a loading dose of PH FDC SC is required (see Section 6.1.1).

After surgery, radiotherapy is to be given as clinically indicated *as per radiotherapy guidelines following the institutional standards*. The selected radiotherapy regimen

should be initiated within 4–*6* weeks after surgery*, ideally after wound healing*. *Adjuvant HER2-targeted therapy should be delivered concurrently with radiotherapy in the run-in period and the selected radiotherapy regimen should not last longer than 5 weeks.* In the event of delays/ interruptions of radiotherapy, PH FDC SC can be provided for one additional cycle during the run-in period (maximum 3 cycles of PH FDC SC during run-in). *The radiotherapy regimen has to be completed within the run-in-period.*

Randomization will occur after completion of the last cycle of radiotherapy and last cycle of PH FDC SC during the run-in period. Sites will be provided with a separate manual of radiotherapy guidelines.

Participants will then be randomized with a ratio of 1:1 into one of two treatment arms in a cross-over treatment period to receive the next 6 cycles of PH FDC SC treatment:

- **Arm C**: 3 cycles of PH FDC SC in the hospital and then 3 cycles of PH FDC SC in the home setting.
- **Arm D**: 3 cycles of PH FDC SC in the home setting and then 3 cycles of PH FDC SC in the hospital.

Randomization in the adjuvant phase will be stratified by disease stage at screening (same as above), type of surgery (conservative or mastectomy), and neoadjuvant chemotherapy option (anthracycline-free or anthracycline-based, as defined in Section 6.3.1).

After the cross-over treatment period, participants will receive the remaining PH FDC SC treatment cycles required to complete the planned 18 cycles of HER2-directed therapy, unless of disease recurrence (per institutional practice or according to the ACS / ASCO Breast Cancer Survivorship Care Guideline; Runowicz et al. 2016; see Section 8.2.7), unacceptable toxicity, or participant withdrawal. Study treatment during this treatment continuation period will be administered either in the hospital or in the home setting as selected by the participant at the end of the crossover period.

Participants can request to change from home administration to hospital administration (and vice-versa) during the treatment continuation period, but not during the treatment cross-over period. This change can occur once only.

4.1.2.2 *Participants Who Have Residual Disease After Surgery*

Participants with pathologic evidence of residual invasive carcinoma in the breast or axillary lymph nodes following completion of preoperative therapy and surgery will enter Arm E:

- **Arm E**: Trastuzumab emtansine IV for 14 cycles.

Trastuzumab emtansine will be administered IV in the hospital as per prescribing information. Trastuzumab emtansine cannot be initiated within ≤ 2 weeks of surgery but must be initiated ≤ 6 weeks of surgery.

Participants in Arm E developing an intolerance to trastuzumab emtansine may require temporary interruption, dose reduction or treatment discontinuation (see Section 6.1.3 and Appendix 3 for more information on the management of participants who experience adverse events during treatment with trastuzumab emtansine). Participants who remain intolerant to trastuzumab emtansine after dose reduction can be discontinued from the study (and be treated as per standard of care) or can remain in the study and be treated with PH FDC SC in the hospital as to complete 14 cycles of HER2-directed adjuvant study treatment in total. This decision is at the discretion of the treating physician. See Appendix 19 for details of the assessments to be conducted in these participants.

Participants who discontinue trastuzumab emtansine because of toxicity that may be attributed to the trastuzumab component (e.g., hypersensitivity, cardiac toxicity, pneumonitis) may not continue to receive PH FDC SC after discontinuation of trastuzumab emtansine.

No adjuvant chemotherapy is allowed after surgery, however, adjuvant hormone, bisphosphonate, and/or radiation therapy are allowed as per local guidelines.

Radiotherapy should be given as clinically indicated and the timing to start the radiotherapy should be based on the local practices, but it must start within 6 weeks after surgery.

All patients will return to the study site for a safety follow-up visit 6–9 months after the last dose of study treatment for assessment of adverse events, and for a pregnancy test for female participants of childbearing age.

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

The participant population included in this study is consistent with the indication for treatment with P+H IV or PH FDC SC, trastuzumab emtansine, and chemotherapy in routine clinical practice and as recommended in local guidelines.

4.2.2 Rationale for Randomized Cross-over Design

Randomization reduces the bias and confounding in the process of participant assignment. Stratified randomization can further prevent the confounding in the interpretation of study endpoints, caused by the known factors of disease stage, neoadjuvant chemotherapy, and type of surgery. The cross-over design allows the participants to be exposed to both the home and in-hospital settings and act as their own control for assessment of clinical outcomes. Exposure to both settings also allows a

realistic, instead of hypothetical, evaluation through the PPQ, which is the primary endpoint of this study.

4.2.3 Rationale for Non-Standard Clinical Outcome Assessments

The PPQ used to assess the primary study endpoint has been developed in clinical trials assessing patient preference for SC administered monoclonal antibodies.

An interview-based assessment was first developed to assess patient preference for trastuzumab SC in a clinical trial of adjuvant trastuzumab SC and IV in HER2+ early breast cancer (Study MO22982, Pivot et al. 2013). Interview questions were based on input from experienced clinicians, chemotherapy nurses and psychologists and were tested with patient volunteers prior to use in the study. The three interview questions identified as most informative in the trastuzumab MO22982 study were then administered as the patient-completed PPQ in a subsequent lymphoma study evaluating preference for SC or IV administered rituximab (PrefMab study, Rummel et al. 2017). Notably, PPQ endpoints collected in this study were considered adequate evidence for preference claims included in rituximab SC product labelling (Rituxan Hycela™; FDA 2017).

The PPQ was also used to evaluate the patient preference for PH FDC SC compared to P+H IV in the PHranceSCa study (Study MO40628, O'Shaughnessy et al. 2020). In this phase II study, 85% (136/160) of people receiving treatment for HER2+ breast cancer preferred treatment under the skin to IV administration due to less time in the clinic and more comfortable treatment administration (O'Shaughnessy et al. 2020; O'Shaughnessy et al. 2021).

A similar PPQ is currently used in the study investigating PH FDC SC administration at home during the coronavirus disease 2019 (COVID-19) pandemic (Study AL42478). The PPQ will be completed by the participant in Study AL42478 using an electronic platform provided by the healthcare provider at the End of Treatment Visit.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

The doses and scheduling of P+H IV in the study are the approved doses for the treatment of early breast cancer. The doses of PH FDC SC selected to be used in this study are consistent with the approved loading (1200 mg pertuzumab/600mg trastuzumab/30,000 units rHuPH20) and maintenance doses of PH FDC SC (600 mg pertuzumab/600 mg trastuzumab/20,000 units rHuPH20) investigated in the pivotal WO40324 FeDeriCa study that confirmed non-inferior Cycle 7 C_{trough} and comparable efficacy of pertuzumab/trastuzumab SC versus pertuzumab/trastuzumab IV in participants with early breast cancer (Tan et al. 2021).

The doses and scheduling of trastuzumab emtansine IV infusions in the study are the approved doses for the treatment of HER2+ advanced breast cancer. The globally approved regimen of trastuzumab emtansine is 3.6 mg/kg q3w as confirmed in Study

TDM4370g/BO21977 (Verma et al. 2012), the pivotal phase III trial comparing trastuzumab emtansine to lapatinib plus capecitabine in participants with HER2+ metastatic breast cancer who were previously treated with trastuzumab and a taxane.

The scheduling of all HER2-targeted treatments (every 3 weeks) is based on pharmacokinetic (PK) studies comparing IV and SC administrations of each molecule (BO22227, Jackisch et al. 2019; and BO30185; Kirschbrown et al. 2019) and the approved scheduling for the administration of P+H IV and of trastuzumab for SC injection.

Participants experiencing severe hypersensitivity reactions should be discontinued from study treatment but maintained in the schedule of activities unless consent is withdrawn.

Refer to the PH FDC SC, pertuzumab, and trastuzumab emtansine Investigator's Brochures, and trastuzumab SmPC, 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 visit shown in the schedule of activities (see Section 1.3).

The end of this study is defined as the date of the last scheduled procedure shown in the schedule of activities (i.e., 6–9 months after the last dose of study treatment) for the last participant in the study globally or the date at which the last data point required for statistical analysis (i.e., PPQ, HRQoL, and HCPQ) or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur approximately 18 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

The total duration of study participation for an individual is expected to be approximately 1.5 to 2 years.

5. STUDY POPULATION

Approximately 330 participants with HER2+ early or locally advanced/inflammatory breast cancer will be enrolled in this study.

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

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

5.1.1 General Inclusion Criteria

- Signed Informed Consent Form
- Age ≥ 18 years at the time of signing Informed Consent Form
- Ability to comply with the study protocol
- Eastern Cooperative Oncology Group (ECOG) performance status 0–1 (Appendix 12)
- Intact skin at planned site of SC injections (thigh)
- Left ventricular ejection fraction (LVEF) ≥ 55% by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA). If the participant has not had an LVEF measured in the last 12 weeks, an ECHO or MUGA should be performed at the screening visit (Appendix 16)
- Negative human immunodeficiency virus (HIV) test at screening with the following exception: participants with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥ 200/µL, have an undetectable viral load and provided that they have not had a history of AIDS-defining opportunistic infections within 12 months prior to randomization. Investigators need to consider potential drug-drug interactions between study treatment and anti-retroviral therapies before enrolling participants
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Positive hepatitis B surface antibody (HbsAb) test at screening, or negative HbsAb at screening accompanied by either of the following:
    - Negative total hepatitis B core antibody (HbcAb)
    - Positive total HbcAb test followed by a negative (per local laboratory definition) hepatitis B virus (HBV) DNA test
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

    The HCV RNA test is only required for participants who have a positive HCV antibody test.
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use *non-hormonal* contraception and agree to refrain from donating eggs as defined below:

    Female participants must remain abstinent or use *non-hormonal* contraceptive methods with a failure rate of < 1% per year, or two effective contraceptive methods during the treatment period and for 7 months after the final dose of the study treatment.

    Female participants must refrain from donating eggs during this same period.

    A female participant is considered to be of childbearing potential if she is post-menarchal, has not reached a post-menopausal state (≥ 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). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. 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 (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate), *and* copper intrauterine devices*. Hormonal contraceptives are not allowed.*

Patients who have had a progesterone-coated device in place prior to screening are not required to have it removed. However, newly inserted devices after screening should not contain estrogen or progesterone.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not adequate methods of contraception. 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.

Female participants of childbearing potential must have a negative serum pregnancy test result within seven days prior to initiation of study treatment

- For male participants: agreement 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, male participants must remain abstinent or use a condom during the treatment period and for 7 months after the final dose of study treatment to avoid exposing the embryo. Male participants 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 post-ovulation 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.

5.1.2 Disease-specific Inclusion Criteria

- Female and male participants with stage II-IIIC early or locally advanced/inflammatory HER2+ breast cancer. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests or a locally validated HER2 test by laboratories with demonstrated proficiency.

- Primary tumor > 2 cm in diameter, or node-positive disease (clinically or on imaging).
- HER2+ breast cancer confirmed by a local laboratory prior to study enrollment. HER2+ status will be determined based on pretreatment breast biopsy material and defined as 3+ by Immunohistochemistry (IHC) and/or positive by HER2 amplification by *in situ* hybridization (ISH) following American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines 2018 and updates (Wolff et al. 2018).

    Participants with multifocal tumor (more than one tumor confined to the same quadrant as the primary tumor) are eligible and at least one focus should be sampled and confirmed as HER2 positive as per clinical practices
- Hormone receptor status of the primary tumor determined by local assessment following ASCO/CAP guidelines 2020 and updates (Allison et al. 2020). Hormone receptor status may be either positive (i.e., estrogen receptor [ER]-positive and/or progesterone receptor [PgR]-positive) or negative (i.e., ER-negative and PgR-negative).
- Agreement to undergo mastectomy or breast conserving surgery after neoadjuvant therapy, including the axillary nodes (sentinels and/or not sentinels).
- Availability of formalin-fixed, paraffin-embedded (FFPE) tumor tissue block for local confirmation of HER2 and hormone receptor status following current ASCO/CAP guidelines.

Note: The neoadjuvant chemotherapy regimen (including type and sequencing of selected agents) is at the discretion of the treating physician and participant based on the three alternatives of this study.

5.1.3 Inclusion Criteria for Treatment with Adjuvant PH FDC SC

- Completed the neoadjuvant phase of this study and underwent surgery, and achieved pCR, defined as eradication of invasive disease in the breast and axilla (i.e., ypT0/Tis ypN0) according to the current American Joint Committee on Cancer (AJCC) staging system classification (FDA 2020), and using the resected specimen by the local pathologist on the basis of guidelines to be provided in a Pathology Manual
- Adequate wound healing after breast cancer surgery per investigator's assessment to allow initiation of study treatment within ≤ 9 weeks of last systemic neoadjuvant therapy

5.2 EXCLUSION CRITERIA

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

5.2.1 General Exclusion Criteria

- Stage IV (metastatic) breast cancer

- History of concurrent or previously treated non-breast malignancies except for appropriately treated 1) non-melanoma skin cancer and/or 2) *in situ* carcinomas, including cervix, colon, and skin. A participant with previous invasive non-breast cancer is eligible provided he/she has been disease free for more than 5 years
- Participants who are pregnant or breastfeeding or intending to become pregnant during the study or within 7 months after the final dose of study treatments.

  Female participants of childbearing potential must have a negative serum pregnancy test result within seven days prior to initiation of study treatment
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Active, unresolved infections at screening requiring treatment. Participants with any severe infection within 28 days prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infections should not be enrolled in the trial (in the current situation, this also applies to participants with suspected or confirmed COVID-19 infection)
- Participants who may have had a recent episode of thromboembolism and are still trying to optimize the anticoagulation dose and/or have not normalized their International Normalized Ratio (INR)
- Serious cardiac illness or medical conditions including, but not confined to, the following:
  - History of NCI CTCAE v5.0 Grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) Class ≥ II
  - 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 II] or third-degree AV-block)
  - Serious cardiac arrhythmia or severe conduction abnormality not controlled by adequate medication
  - Angina pectoris requiring anti-angina medication
  - Clinically significant valvular heart disease
  - Evidence of transmural infarction on electrocardiogram (ECG)
  - Evidence of myocardial infarction within 12 months prior to enrollment
  - Poorly controlled hypertension (e.g., systolic > 180 mm Hg or diastolic > 100 mmHg)
  - Significant symptoms (Grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia while or since receiving preoperative therapy
  - Requirement for continuous oxygen therapy
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD],

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 sudden unexplained death or long QT syndrome.

- Inadequate bone marrow function, defined by any of:
    - Participants who have an absolute neutrophil count (ANC) < 1.5 x 10^9/L
    - Platelet count < 100 x 10^9/L
    - Hemoglobin < 9 g/dL
- Impaired liver function, defined by any of:
    - Serum (total) bilirubin > 1.25 x upper limit of normal (ULN). In case of Gilbert's syndrome: a total bilirubin of 2 x ULN is permitted.
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 1.25 x ULN
    - Albumin < 25 g/L
- Renal function with creatinine clearance < 50 mL/min using the Cockroft-Gault formula and serum creatinine > 1.5 x ULN
- Major surgical procedure unrelated to breast cancer within 28 days prior to study entry or anticipation of the need for major surgery during the course of study treatment
- Current severe, uncontrolled systemic disease that may interfere with planned treatment (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound-healing disorders)
- Any serious medical condition or abnormality in clinical laboratory tests that precludes an individual's safe participation in and completion of the study
- Treatment with a live vaccine (e.g., FluMist) in the 30 days prior to initiation of study treatment, or anticipation of need for such a vaccine during treatment or within 90 days after the final dose of study treatment
- Known active liver disease, for example, active viral hepatitis infection (i.e., hepatitis B or hepatitis C), autoimmune hepatic disorders, or sclerosing cholangitis
- Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins or a history of severe allergic or immunological reactions, e.g., difficult to control asthma
- Current chronic daily treatment with corticosteroids (dose >10 mg methylprednisolone or equivalent excluding inhaled steroids)
- Assessment by the investigator as being unable or unwilling to comply with the requirements of the protocol

5.2.2 Cancer-specific Exclusion Criteria for Neoadjuvant Phase

- Participants who have received any previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy [selective

estrogen receptor modulators, aromatase inhibitors], and antitumor vaccines for treatment or prevention of breast cancer), or previous chest irradiation (radiation therapy) for the treatment of cancer

- Participants who have a past history of ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS) if they have received any systemic therapy for its treatment or radiation therapy to the ipsi- or contralateral breast cancer. Participants are allowed to enter the study if treated with surgery alone
- Participants with high-risk for breast cancer who have received chemopreventive drugs in the past are not allowed to enter the study
- Participants with multicentric (multiple tumors involving more than one quadrant) breast cancer, unless all tumors are HER2+
- Participants with bilateral breast cancer
- Participants who have undergone an excisional biopsy of primary tumor and/or axillary lymph nodes
- Axillary lymph node dissection (ALND) prior to initiation of neoadjuvant therapy. Participants with clinically negative axilla (by physical examination and radiographic imaging) may undergo a core or needle biopsy procedure prior to neoadjuvant systemic therapy if in keeping with local practice
- Sentinel lymph node biopsy (SLNB) prior to neoadjuvant therapy

5.2.3 Exclusion Criterion for Treatment with Adjuvant Trastuzumab Emtansine (Arm E)

- Current Grade ≥ 3 peripheral neuropathy (according to the NCI CTCAE v5.0)

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

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 5.1.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion. Individuals must re-sign the consent form prior to

rescreening. The investigator will maintain a record of reasons for screen failure (see Section 8).

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION

The following conditions may allow a participant to be enrolled/randomized/administer study treatment once the conditions have resolved and the participant is otherwise eligible for participation in the study:

- Participants who have had a serious infection requiring oral or IV antibiotics within 28 days prior to screening trial (in the current situation, this would also apply to participants with suspected or confirmed COVID-19 infection).

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

Study treatment refers to the combination of treatments assigned to participants as part of this study (i.e., fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration [PH FDC SC], alone or with chemotherapy; pertuzumab and trastuzumab IV [P+H IV] plus chemotherapy; and trastuzumab emtansine).

The investigational medicinal products (IMPs) for this study are PH FDC SC (loading dose configuration and maintenance dose configuration, see Section 6.1.1), P+H IV, and trastuzumab emtansine.

Appendix 20 identifies all investigational medicinal products and auxiliary medicinal products (AxMPs) for this study.

All the IMPs will be provided by the Sponsor free of charge.

Chemotherapy drugs and endocrine therapy (Section 6.1.4), pre-medications (Section 6.1.5) and anaphylaxis medications (Section 6.1.6) are regarded as *AxMPs*. *AxMPs* will be obtained locally by the investigational sites or will be provided by the Sponsor as per country requirements.

Study drug supplies will be labelled in accordance with applicable legal requirements and will be printed in the local language. Study drug supplies should not be used beyond the expiration date provided by the manufacturer.

6.1 STUDY TREATMENTS ADMINISTERED

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

Table 7 Study Treatment Description

	PH FDC SC (Loading dose)	PH FDC SC (Maintenance dose)	Pertuzumab IV	Trastuzumab IV	Trastuzumab emtansine IV	Chemotherapy and endocrine therapy
Use	Experimental	Experimental	Experimental	Experimental	Experimental	Background therapy
Type of medicinal product	IMP	IMP	IMP	IMP	IMP	*AxMP*
Drug form	Liquid	Liquid	Liquid	Freeze-dried preparations	Sterile powder	Refer to local prescribing information for docetaxel, carboplatin, doxorubicin, paclitaxel, cyclophosphamide, and endocrine therapy
Unit Dose Strengths	15 mL of solution	10 mL of solution	420 mg/vial	150 mg/vial	160 mg/vial	
Dosage Levels	1200 mg of pertuzumab and 600 mg of trastuzumab	600 mg of pertuzumab and 600 mg of trastuzumab	840 mg (Loading dose) or 420 mg (Maintenance dose)	8 mg/kg (Loading dose) or 6 mg/kg (Maintenance dose)	3.6 mg/kg given as an intravenous infusion	
Formulations	L-histidine/L-histidine-HCl monohydrate, α, α-trehalose dihydrate, Sucrose, L-methionine, Polysorbate 20, rHuPH20 (2000 IU/mL)	L-histidine/L-histidine-HCl monohydrate, α, α-trehalose dihydrate, Sucrose, L-methionine, Polysorbate 20, rHuPH20 (2000 IU/mL)	L-histidine acetate, sucrose, polysorbate 20 at pH 6.0	histidine/histidine-HCl; α, α-trehalose dehydrate; polysorbate 20	Trastuzumab emtansine, sucrose, sodium succinate and polysorbate 20	
Packaging	15 mL vial	10 mL vial	20 mL vial	15 mL vial	20 mL vial	
Labeling	Per local requirements					
Route of administration	SC injection	SC injection	IV infusion	IV infusion	IV infusion	
Source	Sponsor	Sponsor	Sponsor	Sponsor	Sponsor	Site or Sponsor

AxMP = auxiliary medical product; IMP = investigational medicinal product; IV = intravenous injection; PH FDC SC = fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration; SC = subcutaneous injection.

For information on the formulation and handling of the PH FDC SC, see the PH FDC SC Investigator's Brochure.

For information on the packaging, storage and dispensing of pertuzumab for IV infusion, see the current pertuzumab Investigator's Brochure.

For information on the packaging, storage, and dispensing of trastuzumab for IV infusion, see the current trastuzumab SmPC.

For information on the packaging, storage, and dispensing of trastuzumab emtansine for IV infusion, see the current trastuzumab emtansine Investigator's Brochure.

A Mobile Clinical Services Training Manual is provided to participating study sites for reference only and is specifically intended as training and instruction material for the HCPs preparing and administering PH FDC SC doses in the home setting, see Appendix 15. The manuals do not replace the protocol.

The treatment regimens are summarized in Section 4.1.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 2.

6.1.1 PH FDC SC Loading and Maintenance Dose

PH FDC SC is given as a fixed dose (i.e., non-weight based). Two dosage configurations of PH FDC SC may be administered in the study: a 15 mL loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab and a 10 mL maintenance dose consisting of 600 mg pertuzumab and 600 mg trastuzumab. Participants who have had ≥ 6 weeks since their last pertuzumab and trastuzumab treatment (PH FDC SC or P+H IV) must receive a loading dose before continuing with maintenance doses for subsequent administrations.

PH FDC SC is administered by SC injection by the HCP in the home setting or in the hospital on Day 1 of each 3-week treatment cycle. Self-administration is not allowed. Participants should be monitored for 30 minutes after their first dose of PH FDC SC and if another loading dose is required during the study. Participants should be monitored for 15 minutes following subsequent administrations. Participants can be observed for longer periods at the discretion of the HCP or, if necessary, as per local requirements.

Pre-medication with antipyretics, antihistamines, or corticosteroids, according to local practice and investigator discretion, may be administered before PH FDC SC administration.

PH FDC SC should be administered by an HCP after proper training in SC injection technique (See Appendix 15).

PH FDC SC vials must be stored in a refrigerator at 2 °C to 8 °C (36 °F to 46 °F) in the original carton to protect from light until time of use.

Medications to treat hypersensitivity reactions (e.g., H1-receptor or H2-receptor antagonists and steroids) must be available for immediate use (see Section 6.1.6).

For injection-related reactions, the injection should be slowed or paused if the participant experiences symptoms.

6.1.2 Pertuzumab and Trastuzumab

The order of administration of pertuzumab IV and trastuzumab IV is according to investigator preference.

Pertuzumab is given as a fixed non–weight-based dose of 840-mg IV administered as loading dose and then 420-mg IV administered as maintenance dose every 3 weeks. Participants who have had ≥ 6 weeks since their last study treatment with pertuzumab during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

Pertuzumab IV loading dose (if required) will be administered as a 60-minute infusion (± 10 minutes), followed by an observation period of 60 minutes. If the loading dose infusion is well tolerated, subsequent maintenance doses can be administered over a period of 30 minutes (± 10 minutes) with an observation period of 30 minutes. Participants can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements.

Pre-medication with antipyretics, antihistamines, or corticosteroids, according to local practice and investigator discretion, may be administered before pertuzumab IV administration.

For information on the packaging, storage and dispensing of pertuzumab IV, see the current pertuzumab Investigator's Brochure.

Trastuzumab is given as an 8-mg/kg IV administered as loading dose and then 6-mg/kg IV administered as maintenance dose every 3 weeks. Participants who have had ≥ 6 weeks since their last study treatment with trastuzumab during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

Trastuzumab IV loading dose (if required) will be administered as an infusion over approximately 90 (± 10) minutes after which the participant must be observed for 60 minutes. If the loading dose is well tolerated, subsequent maintenance doses can be administered as 30-minute infusions (± 10 minutes) followed by an observation period of 30 minutes. Participants can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements.

Pre-medication with antipyretics, antihistamines, or corticosteroids may be administered before trastuzumab IV administration.

If variation in the participant's weight of ≥ ± 10% compared with study screening occurs, the trastuzumab IV dose will be recalculated. Weight at the time the dose is recalculated will be considered as baseline for subsequent evaluations of degree of weight change with respect to trastuzumab IV dose modification requirements.

For information on the packaging, storage, and dispensing of trastuzumab IV, see the current trastuzumab SmPC.

6.1.3 Trastuzumab Emtansine

Trastuzumab emtansine is given as a vial containing 160 mg powder for concentrate for solution for infusion. After reconstitution, one vial of 8 mL solution contains 20 mg/mL of trastuzumab emtansine. For information on the trastuzumab emtansine formulation, dosage and administration; see the Pharmacy Manual and the trastuzumab emtansine Investigator's Brochure.

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by IV infusion, q3w. The dose of trastuzumab emtansine will be administered based on the participant's baseline weight *after surgery*. Weight will be measured at each visit (or in the 3 days prior) and dose must be re-adjusted for weight changes ≥ 10% compared to the previous visit or baseline. Administration may be delayed to assess or treat AEs. If trastuzumab emtansine is discontinued because of toxicity, it should not be re-administered.

The initial dose should be administered as a 90-minute (± 10 minutes) intravenous infusion. Participants should be observed during the infusion and for at least 90 minutes following the initial infusion for fever, chills, or other infusion-related reactions. The infusion site should be closely monitored for possible subcutaneous infiltration during administration. If the prior infusion was well tolerated, subsequent doses of trastuzumab emtansine may be administered as 30-minute (± 10 minutes) infusions. Participants should be observed during the infusion and for at least 30 minutes after infusion.

Pre-medication with antipyretics, antihistamines, or corticosteroids, according to local practice and investigator discretion, may be administered before trastuzumab emtansine administration.

Trastuzumab emtansine cannot be initiated within ≤ 2 weeks of surgery but must be initiated ≤ 6 weeks of surgery.

Trastuzumab emtansine IV dose should not be re-escalated after a dose reduction is made. If a planned dose is delayed or missed, it should be administered as soon as possible; do not wait until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion may be administered at the dose and rate the participant tolerated in the most recent infusion.

The infusion rate of trastuzumab emtansine should be slowed or interrupted if the participant develops an infusion-related reaction. Permanently discontinue trastuzumab emtansine for life-threatening infusion-related reactions.

Management of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction, thrombocytopenia, pulmonary toxicity, or peripheral neuropathy may require temporary interruption, dose reduction or treatment discontinuation.

Recommended dose reduction schedule for adverse events:

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Trastuzumab emtansine dose should not be re-escalated after a dose reduction is made. See Appendix 3 for more information on the management of participants who experience adverse events during treatment with trastuzumab emtansine.

Participants in Arm E who remain intolerant to trastuzumab emtansine after dose reduction can be discontinued from the study (and be treated as per standard of care) or can remain in the study and be treated with PH FDC SC in the hospital as to complete 14 cycles of HER2-directed adjuvant study treatment in total. This decision is at the discretion of the treating physician. See Appendix 19 for details of the assessments to be conducted in these participants.

Participants who discontinue trastuzumab emtansine because of toxicity that may be attributed to the trastuzumab component (e.g., hypersensitivity, cardiac toxicity, pneumonitis) may not continue to receive PH FDC SC after discontinuation of trastuzumab emtansine.

6.1.4 Chemotherapy and Endocrine Therapy

Doxorubicin and cyclophosphamide treatments (neoadjuvant chemotherapy options 2 and 3) should be given before HER2-targetting therapies (PH FDC SC or P+H IV). Taxanes (docetaxel or paclitaxel) and carboplatin should be given after HER2-targetting therapies (see Figure 1).

The neoadjuvant chemotherapeutic treatments such as carboplatin, doxorubicin, cyclophosphamide, docetaxel, and paclitaxel are regarded as $AxMPs$. Chemotherapeutic drugs and endocrine therapy will be administered in accordance with local prescribing information according to the study scheme (see Figure 1 and Section 4.1).

Refer to the respective SmPC or other appropriate local reference document for information on formulation, preparation, administration, contraindications, and participant monitoring.

6.1.5 Pre-medications

Pre-medications and other supportive medications are regarded as $AxMPs$. All participants may receive medications, at the discretion of the treating physician, to treat or prevent allergic or infusion reactions as mentioned in Section 6.8.2, permitted therapies.

If pre-medication is required prior to administration of PH FDC SC in the home setting, the treating physician should prescribe pre-medications in tablet form.

6.1.6 Anaphylaxis Medication

Anaphylaxis medications listed in Section 6.8.2 are permitted and are regarded as $AxMPs$. These are to be used only by the HCP in the event of a severe hypersensitivity reaction during or after administration of study treatment (PH FDC SC, pertuzumab IV, trastuzumab IV, or trastuzumab emtansine).

Anaphylaxis kits are currently used in the study investigating the SC administration of PH FDC SC at home during the COVID-19 pandemic (Study AL42478).

The sponsor will provide anaphylaxis kits for use in the home setting. These kits must be available before the first home administration of PH FDC SC and should only be used by the mobile healthcare professional. Additional kits will be provided if kits expire, are damaged or are used during the study.

Anaphylaxis kits will contain:

- x2 Diphenhydramine (30 mg [2 mL ampoule]) for intramuscular (IM*) injection or equivalent
- x1 Hydrocortisone sodium succinate (100 mg [2 mL vial]) for IM injection or equivalent
- x2 Epinephrine, USP Auto-Injector 0.3 mg for IM injection or equivalent

**IM needles will be supplied by the mobile healthcare professional.*

See the Mobile Clinical Services Training Manual for guidance on the assessments to conduct if anaphylaxis medications are administered in the home setting.

If anaphylaxis medications are administered during site administration of study treatments, participants should be treated according to local standard of care.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist or HCPs) 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) to confirm the shipment condition and content. Any damaged shipments will be replaced. *Temperature conditions for all IMPs will be monitored during transit, and any discrepancies will be 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 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.

For home administration of PH FDC SC, the PH FDC SC, pre-medication (if applicable), and anaphylactic medication will be delivered by courier from the site to the participant's home at the time of the scheduled visit and received by the mobile healthcare professional. PH FDC SC and pre-medication (if applicable) will be delivered at every home visit. Anaphylactic medication will be delivered at the first home visit in a locked medication box and will be kept at room temperature in the patient's home. Only the mobile healthcare professional will have the code for the lock box. If replacements of the medications are needed (i.e., because they expired or were used), the site will provide the replacement medication with the next shipment of PH FDC SC to the patient's home.

The mobile healthcare professional will confirm the supplies were handled appropriately during transit and will be responsible for returning any used and unused drugs and other supplies to the study site. See the Mobile Clinical Services Training Manual for more

information on the delivery and handling of study treatments and other medications for administration in the home setting.

Refer to the Pharmacy Manual and/or the PH FDC SC, pertuzumab, and trastuzumab emtansine Investigator's Brochures, and the trastuzumab SmPC, 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 and treatment assignment from an IxRS. Randomization in both the neoadjuvant and adjuvant phases will occur through the use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm.

During the neoadjuvant phase, the enrolled participants will be randomly allocated, in a ratio of 1:2, to Arm A or Arm B (defined in Section 4.1.1). Randomization in the neoadjuvant phase will be stratified by disease stage at screening (operable [T2–3, N0–1, M0*, or T1/N1/M0*], locally advanced [*T1*–3, N2–3, M0 or T4a–c, any N, M0], or inflammatory [T4d, any N, M0]) and neoadjuvant chemotherapy option (see Section 4.1.1: anthracycline-free [chemotherapy option 1] or anthracycline-based [chemotherapy options 2 or 3]).

After completing their neoadjuvant therapy, participants from both arms will undergo surgical resection for early or locally advance*d* HER2+ breast cancer (if eligible for surgery). Participants who have achieved pCR after surgery will continue adjuvant treatment with PH FDC SC, while participants with pathologic evidence of residual invasive carcinoma in the breast or axillary lymph nodes following completion of preoperative therapy and surgery will undergo adjuvant treatment with trastuzumab emtansine IV in Arm E (see Section 4.1.2).

Participants who have achieved pCR after surgery will receive the first 2 cycles of PH FDC SC in the hospital. Then, participants will be randomized to Arm C or Arm D (see Section 4.1.2) with a ratio of 1:1 in a cross-over treatment period to receive the next 6 cycles of PH FDC SC treatment. Randomization will occur after completion of the last cycle of radiotherapy (if applicable, see Section 4.1.2) and last cycle of PH FDC SC (during the run-in period). Randomization in the adjuvant phase will be stratified by disease stage at screening (same as above), type of surgery (conservative or mastectomy), and neoadjuvant chemotherapy option (same as above).

After the cross-over treatment period, participants will receive the remaining PH FDC SC treatment cycles as described in Section 4.1.2.

6.4 STUDY TREATMENT COMPLIANCE

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed.

When participants are dosed at the site or at home, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the electronic Case Report Form (eCRF). The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

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 *accidental overdose or medication error*, along with any associated adverse events, should be reported as described in Appendix 2.

6.5 DOSE MODIFICATION

Modification of the PH FDC SC dose or P+H IV dose is not permitted.

For trastuzumab emtansine, management of symptomatic adverse events may require temporary interruption, dose reduction, or treatment discontinuation of trastuzumab emtansine IV as per guidelines provided in local label. Trastuzumab emtansine IV dose should not be re-escalated after a dose reduction is made. Refer to Section 6.1.3 for details of dose modification.

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

Currently, the Sponsor does not have any plans to provide Roche IMPs (PH FDC SC, pertuzumab IV, trastuzumab IV, trastuzumab emtansine IV) or any other study treatments to participants who have completed the study. The Sponsor may evaluate whether to continue providing PH FDC SC, pertuzumab IV, trastuzumab IV, trastuzumab emtansine IV in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, 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. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 2.

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

1. Contact the Medical Monitor

2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until the study treatment can no longer be detected systemically (at least 28 days).

6.8 CONCOMITANT THERAPY

Any medication (including over-the-counter or prescription medicines, vitamins, and herbal supplements) and vaccine used by a participant in addition to protocol–mandated treatment from 7 days prior to initiation of study treatment to the end of the treatment visit must be recorded on the concomitant medications form (CMF) and 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 related to concomitant or prior therapy.

6.8.1 Surgery

Participants in both arms are scheduled to undergo surgery after completing their neoadjuvant therapy. Participants may undergo breast-conserving surgery or mastectomy according to routine clinical practice. The surgery cannot be performed ≤ 2 weeks from the last systemic neoadjuvant therapy and must be performed ≤ 6 weeks after the last systemic neoadjuvant therapy.

If surgery is significantly delayed (>42 days since the last P+H IV or PH FDC SC administration), a maximum of two additional cycles of P+H IV or PH FDC SC (depending on the treatment arm (A or B) assigned to the participant at randomization), can be administered at the investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. See Appendix 18 for details of the assessments that should be conducted for participants who require additional cycles of P+H IV or PH FDC SC due to a delay with surgery.

Before starting neoadjuvant treatment, the primary tumor site should be marked using the method, which is routine clinical practice (e.g., skin tattoo or surgical clip) to enable appropriate surgical excision in case of tumor regression during neoadjuvant therapy. SLNB is not allowed prior to neoadjuvant therapy.

Surgical management options for axillary lymph nodes include SLNB (after neoadjuvant treatment) and ALND of Level I and II lymphatics at the moment of breast surgery. The choice of the axillary procedure will be based on the clinical status of axilla, T stage, and local practice.

In participants with clinically negative axillary nodes at screening, axillary surgical management after completion of neoadjuvant therapy should include SLNB or ALND. SLNB is the preferred method of axillary surgical management, if an experienced team is available. If SLNB is conducted, it is strongly recommended that more than one lymph node (2 to 3 minimum) be removed. All participants with positive macrometastases in sentinel nodes should undergo ALND regardless of the number of positive nodes, and it is recommended that at least 10 lymph nodes be removed for pathologic examination.

Participants with clinically positive axillary lymph nodes at screening should undergo ALND at time of definitive surgery (after neoadjuvant therapy). It is recommended that at least 10 lymph nodes be removed for pathologic examination.

For sentinel nodes involving the internal mammary chain, refer to local, national, or international guidelines.

Level III axillary dissections should only be performed for participants with gross disease in the Level II nodes.

Investigators may follow more up-to-date guidelines on axilla management based on emerging data once they have been incorporated into institutional, local, national, or international guidelines (e.g., NCCN, ESMO, St. Gallen, Lisbon Conference, or American Society of Clinical Oncology [ASCO] Clinical Practice Guidelines).

Following completion of neoadjuvant therapy and surgery, pCR (ypT0/is, ypN0) will be established via local review. Pathologists who review study specimens must utilize the evaluations and assessments outlined in the Pathology Manual. Further details regarding pathology evaluation and assessment are outlined in the Pathology Manual and in Section 8.4.

For participants not eligible for surgery (for example, those whose tumor remains inoperable after neoadjuvant treatment), locoregional and/or systemic management will be done as per local standard practice. These participants will be withdrawn from study treatment and will remain on study for follow-up of secondary and exploratory endpoints unless they have withdrawn consent from study participation.

6.8.2 Permitted Therapy

Participants are permitted to use the following therapies during the study:

- Hormone therapy for breast cancer as per local guidelines
- Bisphosphonate therapy as per local guidelines

- Adjuvant radiotherapy for breast cancer. After surgery, radiotherapy is to be given as clinically indicated and as per local practice or institutional standards

  For participants who have achieved pCR, *the selected radiotherapy regimen should be initiated within 4–6 weeks after surgery* and should not last longer than 5 weeks (see Section 4.1.2)
- Contraception: acceptable methods of contraception must be used when the female participant is of childbearing potential (i.e., is post-menarchal, has not reached a post-menopausal state [post-menopausal defined as ≥ 12 continuous months of amenorrhea with no identified cause other than menopause], and has not undergone surgical sterilization [removal of ovaries and/or uterus]). Acceptable methods of contraception are described in Section 5.1.1
- H1-receptor or H2-receptor antagonists (e.g., diphenhydramine, cimetidine)
- Cardiovascular medications including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers and diuretics, beta blockers, calcium channel blockers, digoxin, thrombocyte aggregation inhibitors
- Analgesics / anti-inflammatories (e.g., paracetamol / acetaminophen, meperidine, opioids)
- 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.
- Standard therapies for pre-existing medical conditions and medical or surgical complications
- Any medication intended solely for supportive care (e.g., analgesics, antidiarrheals, antidepressants) at the investigator's discretion
- Colony-stimulating factors (e.g., G-CSF)
- Blood transfusions at the investigator's discretion
- Gonadotropin-releasing hormone agonists for fertility preservation
- Vitamin and mineral supplements
- Bone density modifying agents (to be used in accordance with the approved labelled indication and/or nationally recognized treatment guidelines)
- COVID-19 vaccine could be administered at the investigator's discretion as the situation for every participant is different in different parts of the world
- 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-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per institutional standard practice. Serious infusion-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).

6.8.3 Cautionary Therapy

6.8.3.1 Medications Given with Precaution due to Effects Related to CYP Enzymes

In vitro data suggest that DM1, a component of trastuzumab emtansine is metabolized mainly by cytochrome p450 (CYP) CYP3A4 and, to a lesser extent, by CYP3A5, and there is a moderate to high potential for drug-drug interaction with any medication that is metabolized by or strongly inhibits or induces these enzymes. DM1 does not induce or inhibit P450-mediated metabolism in vitro. Therefore, the medications listed below should be avoided. If use of one of these medications is necessary, the risks and benefits should be assessed by the investigator prior to concomitant administration with trastuzumab emtansine. The Medical Monitor is available to advise as needed.

- Strong CYP3A4/CYP3A5 inhibitors, including, but not limited to, ketoconazole and itraconazole

The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise if questions arise regarding medications not listed above. If a strong CYP3A4/5 inhibitor needs to be co-administered with trastuzumab emtansine, patients should be closely monitored for adverse reactions."

6.8.3.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their PK, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

6.8.3.3 Therapies Given for Chemotherapy Induced Thrombocytopenia

Concomitant use of therapies for prevention and treatment of thrombocytopenia induced by chemotherapy, e.g., thrombopoietin receptor agonists, recombinant thrombopoietins, recombinant interleukin, should be avoided. Adherence to the relevant safety management guidelines to institute appropriate dose modifications of trastuzumab emtansine in case of thrombocytopenia is recommended (Appendix 3). If any of those agents needs to be co-administered with trastuzumab emtansine in line with local standard clinical practice, patients should be closely monitored for adverse reactions and overlapping toxicities.

6.8.4 Prohibited Therapy

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

- Any investigational therapy or agent (other than protocol-mandated study treatment) within 28 days prior to initiation of study treatment and during study treatment

- Any anti-cancer treatment other than adjuvant hormone treatment, adjuvant radiotherapy or bone density modifying treatment
- Regular systemic treatment with steroids. Short-term corticosteroid 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.
- Any systemically active oral, injected, or implanted hormonal method of contraception (see Section 5.1.1 or acceptable contraception methods) except for progesterone-coated IUDs that had been previously implanted
- Hormone-replacement therapy
- Use of erythropoiesis-stimulating agents (e.g., erythropoietin)
- Herbal remedies initiated for cancer treatment. Other herbal remedies are discouraged but permitted and must be reported on the appropriate eCRF
- Live attenuated vaccines (e.g., FluMist) in the 30 days prior to initiation of study treatment, during study treatment, and for 90 days after the final dose of study treatment. Treatment with live vaccines is permitted for participants receiving adjuvant treatment with trastuzumab emtansine (Arm E)
- For participants with hormone-receptor positive tumors: Topical estrogens (including any intra-vaginal preparations), megestrol acetate, and selective ER modulators used with prophylactic intent are prohibited. Post-menopausal women with significant vaginal discomfort associated with anti-estrogen therapy may be considered for intermittent use of low-dose topical estrogens if non-prescription methods are unsuccessful at ameliorating symptoms.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 ASSESSMENTS AT THE TREATMENT COMPLETION/DISCONTINUATION VISIT

Participants who complete study treatment (all cycles of chemotherapy and HER2-targeted therapy) or discontinue from all study treatment early will be asked to return to the clinic for a treatment completion / treatment discontinuation visit 28 days (± 7 days) after the final dose of study drug (see Table 4 *or Table 5* for additional details). If a participant has progressive disease or relapse, the visit at which this is determined may be used as the treatment completion/early discontinuation visit.

7.2 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will not 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 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
- Heart failure (NYHA class III or IV)
- Anaphylaxis associated with any of the study drugs
- Participants who experience disease recurrence or progression will be withdrawn from study treatment and referred back to the treating physician
- Participants who experience severe infusion/injection related reactions with P+H IV or PH FDC SC.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

Participants will return to the clinic for a treatment completion / treatment discontinuation visit 28 days (± 7 days) after the final dose of study drug (see Table 4 *or Table 5* for additional details). Anti-cancer treatment for participants who have prematurely discontinued study treatment is at the discretion of the investigator as clinically indicated.

7.3 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.

Every effort should be made to obtain a reason for participant discontinuation from the study. 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. Participants who withdraw from the study will not be replaced.

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.

7.4 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.

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.

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 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), reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at screening. Any vaccine and/or medication (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. 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.

Certain study assessments will be performed by a mobile healthcare professional at the participant's home as per the schedule of activities (see Section 1.3, Table 4) to improve access and convenience for participants participating in the study. The Sponsor will select a healthcare company that will be responsible for providing mobile healthcare professional services for participating sites (the mobile healthcare professional vendor). The mobile healthcare professional vendor is responsible for ensuring that all mobile healthcare professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. The mobile healthcare professional network will communicate with the participant and the participant's site. Mobile healthcare professional visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the mobile healthcare professional. The mobile healthcare professional will contact the participant within 3 business days before the visit, to confirm the time and place of the visit. During home visits, the mobile healthcare professional will complete the study assessments as requested by the study site (in line with the schedule of activities [Table 4]). The mobile healthcare professional will provide the information collected to the treating physician (via phone call) who will determine if the participant should receive the next PH FDC SC

treatment. If required, the study investigator may request the participant attends the hospital for assessment by the treating physician. The schedule of activities (see Section 1.3, Table 4) will specify the assessments that may be performed by a mobile healthcare professional (see also the Mobile Clinical Services Training Manual).

In exceptional circumstances, as approved by the Sponsor, HCPs from study sites may undertake the home health visits instead.

8.1 EFFICACY ASSESSMENTS

Pathologic response will be evaluated after surgery by the pathologists in the local laboratories.

Achievement of pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis ypN0), according to the current AJCC staging system classification (FDA 2020).

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

Physical examination should be conducted as outlined in the schedule of activities (see Section 1.3). A complete physical examination will include, at a minimum, assessments of physical measurements (body weight in kilograms and, at screening only, height in centimeters) and evaluation of the head; eyes; ears; nose; throat; and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. ECOG Performance Status will also be assessed. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited symptom-directed physical examinations including weight should be performed at specified post-screening visits and as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from abnormalities identified at screening should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. *In the adjuvant setting, the mobile HCP should complete the limited physical examinations in accordance with local practice/regulations.*

Physical examinations should be conducted in accordance with institutional practice or the American Cancer Society/American Society of Clinical Oncology Breast Cancer (ACS/ASCO) Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016).

8.2.2 Vital Signs

Vital signs should be conducted as outlined in the schedule of activities (see Section 1.3). Temperature, pulse rate, respiratory rate, and systolic and diastolic

blood pressure will be assessed before and after study treatment administration. Vital signs will be measured once at visits where no study treatment is administered.

Blood pressure, respiratory and pulse measurements will be assessed while the participant is in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests while the participant is in a seated position) will consist of one pulse and one blood pressure measurement.

If anaphylactic medications are administered at the study site due to hypersensitivity and/or anaphylactic reaction, vital signs monitoring will be conducted according to local standard of care.

During home administration of study treatment, if a participant experiences hypersensitivity and/or anaphylactic that necessitate the administration of anaphylactic medications (see Section 6.1.6), blood pressure and respiratory rate will be measured approximately every 5 minutes by the mobile healthcare professional. Pulse rate and oxygen saturation will be continuously monitored using the pulse oximeter. Vital signs will be measured until symptoms have fully resolved or emergency medical services arrive. The mobile healthcare professional will promptly contact the site and specify details of the event.

8.2.3 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 and QT interval. Refer to Appendix 3 for withdrawal criteria and any additional readings that may be necessary.

Lead placement should be as consistent as 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. Digital recordings (if available) will be stored 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 at a particular postdose time point the mean QTcF is >500 ms and/or >60 ms longer than the screening (baseline) value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted at the investigator's discretion. A decision on study drug discontinuation should be made, as described in Appendix 3 (Section A3–2.3). The investigator should also evaluate the participant for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

8.2.4 Cardiac Function

Assessment of cardiac function should be conducted as outlined in the schedule of activities (see Section 1.3). All participants must have a prior LVEF ≥ 55% by ECHO or MUGA scan in order to be eligible for the study. If the participant has not had an LVEF measured in the last 12 weeks, an ECHO or MUGA should be performed at the screening visit. If possible, the same LVEF evaluation method should be used throughout the study for each participant and should be performed and assessed by the same assessor.

All LVEF assessments will be performed during Days 15–21 of 3-week cycles prior to the cycle indicated, LVEF assessment may also be performed on Day 1 of treatment. The results must be available before treatment is administered. Apart from the specified mandatory LVEF assessment, the investigator may request additional assessment based on the individual participant's cardiovascular function with a minimum frequency of 3–4 months.

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 LVEF assessment on more than four occasions within one year.

8.2.5 Clinical Breast Examination

Clinical breast examination should be conducted as outlined in the schedule of activities (see Section 1.3). During the neoadjuvant treatment period, tumor response assessment will be performed at screening, prior to each new cycle of therapy, and at treatment discontinuation (if applicable), by clinical breast examination (mandatory) and other methods of evaluation as per routine clinical practice. Assessment may be done within 3 days prior to treatment day.

All measurable and/or evaluable lesions should be assessed and documented at screening. Tumor assessments performed as 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 defined.

Assessments should be conducted by treating physician in accordance with institutional practice or the American Cancer Society/American Society of Clinical Oncology Breast Cancer (ACS/ASCO) Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016).

8.2.6 Mammograms

Mammograms should be conducted as outlined in the schedule of activities (see Section 1.3). Bilateral mammogram must be obtained at screening and at treatment completion or treatment discontinuation visit. A mammogram prior to surgery (after the last cycle of neoadjuvant treatment) is also required. Participants who have undergone a mastectomy and have had breast reconstruction do not require mammograms.

If the participant's clinical status has not changed, the screening mammogram can be performed up to 42 days prior to the start of treatment. The mammogram at screening, pre-surgery, and treatment completion or discontinuation visit can be replaced by other conventional imaging methods such as magnetic resonance imaging (MRI) or ultrasound as per local medical practice, at the investigator's discretion, but the same method of assessment must be used throughout for an individual participant. If another method is used, this must be performed within the 28-day screening window. If a mammogram has been conducted as part of routine preventive care within 4 months of the treatment completion or discontinuation visit, it may be used in lieu of the end-of-study mammogram.

8.2.7 Diagnosis of Breast Cancer Recurrence or Second Primary Cancer

Diagnosis of breast cancer recurrence or second primary cancer should be conducted as outlined in the schedule of activities (see Section 1.3). All participants must be followed to assess disease recurrence and second primary cancers. The designation of disease recurrence whether local, regional or distant, or a diagnosis of second primary cancer will be conducted per institutional practice or according to ACS / ASCO Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016) but can be made only when clinical, laboratory, radiological and/or histological findings support the diagnosis.

The diagnosis of a breast cancer progression, recurrence or a second primary tumor should be confirmed histologically whenever clinically possible. The earliest date of diagnosis of recurrent disease should be used and recorded. This date should be based on objective clinical, radiological, histological, or cytological evidence. The date of disease recurrence should be reported as the date of first diagnosis of a lesion (i.e., an objective finding), not the date of occurrence of the first symptom or suspicion of progression.

Recurrent disease includes local, regional, and distant recurrence and contralateral invasive breast cancer. Participants who are diagnosed with in situ breast disease or second (non-breast) malignancies should be maintained in regular follow-up wherever possible to fully capture any subsequent recurrent breast cancer events. In cases of diagnostic doubt (e.g., ill-defined, palpable mass in an irradiated breast), histologic or cytologic confirmation of recurrence should be obtained whenever possible.

Some participants may develop a suspicious recurrence that leads quickly to death without the possibility of confirming relapse of disease. Efforts should be made to obtain an autopsy report in such participants.

8.2.8 Clinical Safety Laboratory Assessments

See Appendix 11 for the list of clinical laboratory tests to be performed and the schedule of activities (see Section 1.3) for the timing and frequency. Samples for the laboratory tests will be sent to the study sites local laboratory for analysis.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study treatment 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 judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 11, must be conducted in accordance with the schedule of activities.

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.

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

8.2.9 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 11.

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 treatments (see Section 7).

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 2). 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 study treatment or until it is resolved, whichever is longer and at the time points specified in the schedule of activities (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 Appendix 2. 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 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, the event is assessed as stable by the investigator, the participant is lost to follow-up (as defined in Section 7.4), 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 regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements *for expedited* safety reporting to regulatory *authorities (which includes the use of applicable systems, such as EudraVigilance),* Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

*I*nvestigator 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
PH FDC SC	PH FDC SC Investigator's Brochure
Pertuzumab IV	Pertuzumab Investigator's Brochure
Trastuzumab IV	Trastuzumab E.U. Summary of Product Characteristics
Trastuzumab emtansine IV	Trastuzumab emtansine 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 the Summary of Product Characteristics and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

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

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 Appendix 2 Section A2–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- An asymptomatic decline in LVEF that requires treatment or that leads to discontinuation of study treatment
- Congestive heart failure (CHF)
- 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 Appendix 2 Section A2–7.1)
- 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.

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

8.3.9 Medical Monitors and Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PATHOLOGY

Disease stage will be determined prior to randomization to determine study eligibility and for randomization stratification in the neoadjuvant phase. Tumor staging at screening is not mandatory if the results of staging performed as per local practice, in alignment with national guidelines and as clinically indicated, within 28 days of randomization are available.

Results of HER2 and hormone receptor testing conducted by a local laboratory based on breast tumor tissue obtained prior to initiation of neoadjuvant treatment will be collected to assure study eligibility. Results of previous HER2/hormone receptor status diagnoses can be used to determine eligibility if the sample was tested in the 90 days prior to enrollment. Reassessment of HER2/hormone receptor status is not mandatory in these cases but can be done as per local decision.

After surgery, pathologic response will be assessed by the local pathologist using guidelines provided in a Pathology Manual. See Section 8.1 for the definition of pCR. Molecular assay for analysis of sentinel lymph nodes after neoadjuvant therapy is not allowed.

8.5 PHARMACOKINETICS

Pharmacokinetic parameters are not evaluated in this study.

8.6 PHARMACODYNAMICS

Pharmacodynamic biomarker assessments will not be performed in this study.

8.7 GENETICS

Genetic biomarker assessments will not be performed in this study.

8.8 BIOMARKER ASSESSMENTS

Biomarker assessments will not be performed in this study.

8.9 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed in this study.

8.10 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

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

8.11 CLINICAL OUTCOME ASSESSMENTS

Patient-reported outcome (PRO) and clinician-reported outcome (ClinRO) instruments will be completed to assess participant preference for study treatment administration in the home setting and in the hospital setting, treatment impact on quality of life, and HCPs experience with study treatment administration.

PRO data will be collected through use of the following instruments:

- PPQ: Patient preference data will be collected through the PPQ (Appendix 5).
- HRQoL: Health-related Quality of Life will be assessed based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) completed at specified timepoints throughout the study (Appendix 8).

ClinRO data will be collected through use of the following instruments:

- HCPQ: Healthcare professionals' perception of the use of time/resources and the convenience of administering the treatment will be assessed through HCPQs administered in the neoadjuvant phase (Appendix 6 and Appendix 7) and the adjuvant phase (Appendix 9 and Appendix 10).

8.11.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered (or interviewer-administered if required, such as in cases of participant illiteracy) at specified timepoints during the study (see schedule of activities in Section 1.3). The PRO instruments will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in paper form to enable the appropriate instruments to be administered in the correct order at each specified timepoint.

Participants should be given the following instructions for completing PRO instruments at home:

- Participants should complete the instruments in a quiet area with minimal distractions and disruptions.

- Participants should answer questions to the best of their ability; there are no right or wrong answers.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

During clinic visits and visits conducted by a mobile healthcare professional, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments, estimated to be 5–15 minutes at each specified visit.
- Sites 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 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 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 should ask the participants to complete the item or confirm that the item was intentionally left blank.

ClinRO instruments will be completed at specified timepoints during the study (see schedule of activities in Section 1.3). The instruments will be provided by the Sponsor in paper form. Clinicians must complete the official version of each ClinRO instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.

8.11.2 Description of Clinical Outcome Assessment Instruments

8.11.2.1 Patient Preference Questionnaire

The PPQ was used to evaluate the patient preference for PH FDC SC compared to P+H IV in the PhranceSCa study (Study MO40628, O'Shaughnessy et al. 2020). In this phase II study, 85% (136/160) of people receiving treatment for HER2+ breast cancer preferred SC treatment to IV administration due to less time in the clinic and more comfortable treatment administration (O'Shaughnessy et al. 2020; O'Shaughnessy et al. 2021).

A similar PPQ is currently used in the study investigating the SC administration of PH FDC SC at home during the COVID-19 pandemic (Study AL42478). For the Study

AL42478, the PPQ will be completed at home in its entirety by the participant using an electronic platform provisioned by the healthcare provider at the End of Treatment Visit.

In this study, the PPQ will be given in paper form to participants in Arm C and D following treatment administration on Day 1 of the last cycle in the cross-over period (in the adjuvant treatment phase; Appendix 5). Participants who discontinued study treatment prior to the last cycle of the cross-over period should complete the questionnaire at the time of discontinuation as long as they have received at least one dose PH FDC SC in the home setting.

8.11.2.2 EORTC QLQ-C30

In this study, Health-related Quality of Life (HRQoL) will be assessed based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). This instrument will be completed before treatment is administered on Day 1 of the treatment cycles indicated in Table 1 (neoadjuvant phase, treatment option 1), Table 2 (neoadjuvant phase, treatment option 2), Table 3 (neoadjuvant phase, treatment option 3) and Table 4 (adjuvant phase *Arms C and D*) *or Table 5 (adjuvant phase Arm E)*. The study questionnaire is provided in Appendix 8.

The QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Appendix 8). 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.

8.11.2.3 Healthcare Professional Questionnaire

Two HCPQs will be used to capture the perception of time/resource use and perception of convenience during this study.

One HCPQ will be given during the neoadjuvant phase of this study (HCPQ-neoadjuvant phase) (Appendix 6 and Appendix 7).

The other HCPQ will be given during the adjuvant phase of this study in participants who achieved pCR (HCPQ-adjuvant phase) (Appendix 9 and Appendix 10).

These questionnaires will be completed after administration of each participant’s treatment during the neoadjuvant and adjuvant phase of the study and according to the schedule of activities (see Table 1, Table 2, Table 3, and Table 4).

The HCPQs given during the neoadjuvant and adjuvant phases both have two parts:

- HCPQ – Drug Preparation Area will be completed by an HCP involved in study drug preparation (Appendix 6 [neoadjuvant phase] and Appendix 9 [adjuvant phase]).
- HCPQ – Administering Treatment will be completed by an HCP involved in treatment preparation and/or administration in the treatment area where study drugs are administered (Appendix 7 [neoadjuvant phase] and Appendix 10 [adjuvant phase]).

The HCPQs will be completed by the HCP after preparation and/or administration of the study treatment at the scheduled time point (see Table 1, Table 2, Table 3, and Table 4).

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

There are no additional assessments and procedures requiring separate consent or performed only at participating sites.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary endpoint of this study is the proportion of participants who prefer PH FDC SC administered by an HCP in the home setting compared with the hospital setting during the adjuvant phase. No formal statistical hypotheses will be tested for this study.

The primary analysis will take place when all study participants entering the PH FDC SC cross-over period have completed their last study treatment and all scheduled assessment in the cross-over period. Summaries of secondary study endpoints, EORTC QLQ-C30 responses, selection of treatment administration method for the treatment continuation period, HCPQ responses and planned safety endpoints will be included in the primary analysis.

The final analysis that includes all data collected during the study will be conducted after the end of the study.

9.2 SAMPLE SIZE DETERMINATION

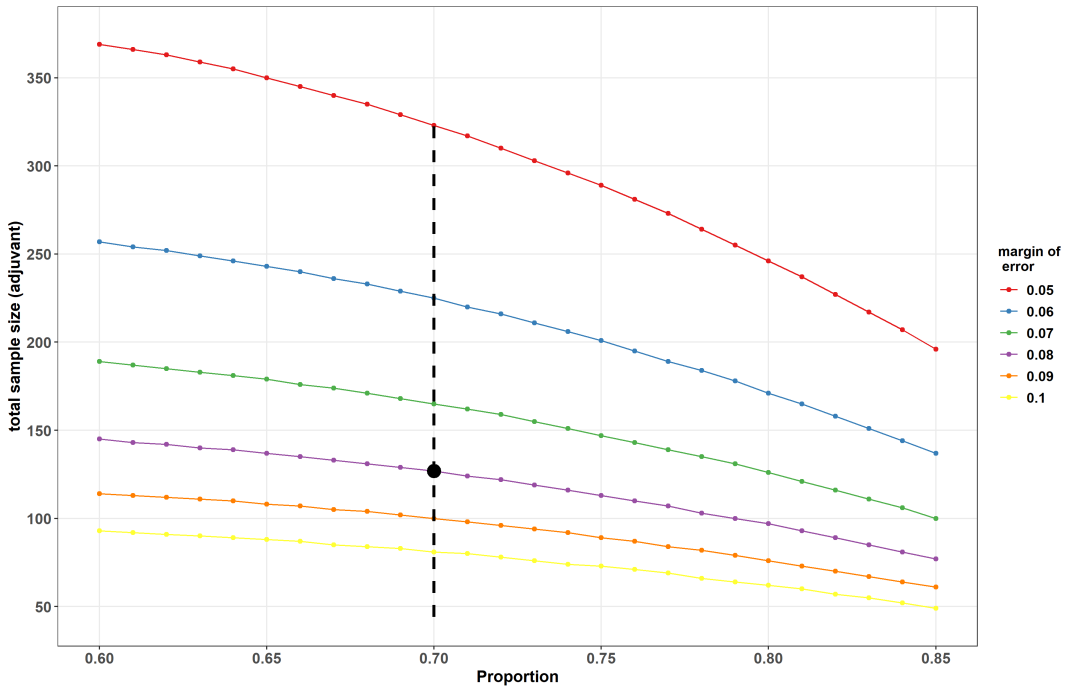
Approximately 330 participants will be enrolled for the neoadjuvant phase of study treatment such that approximately 150 evaluable participants enter Arm C and D and complete the cross-over period.

To achieve a distance approximately 8% from the estimated proportion to 95% confidence interval limits, a total of 128 participants are needed for the evaluation of patient preference rate at the end of the cross-over period, with an underlying assumed preference rate of 70% for the home setting (Figure 2). To allow for 15% dropout during

adjuvant phase and/or non-evaluable PPQ outcome up to the completion of the cross-over period, the study needs approximately 150 participants entering Arm C and D. The planned total enrollment from the neoadjuvant phase would be approximately 330 participants, considering a pCR of 50% (Schneeweiss et al. 2013) after surgery and 8% dropout in the neoadjuvant phase.

Note: “Enrolled” means a participant’s, or their legally acceptable representative’s, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Figure 2 Sample size for estimating one proportion with two-sided 95% CI



9.3 ANALYSIS SETS

The following populations are defined:

Participant Analysis Set	Description
Neoadjuvant analysis set	All participants randomly assigned to study treatment and receiving at least one planned study treatment in the neoadjuvant phase. This analysis set will be used for the analysis of pCR and clinical outcome assessments (HCPQ and HRQoL), as well as for the safety analysis in the neoadjuvant phase.

Participant Analysis Set	Description
Adjuvant analysis set for PH FDC SC cohort	All participants with pCR entering the PH FDC SC cohort in the adjuvant phase and receiving at least one dose of PH FDC SC. This analysis set will be used for the analysis of safety, HRQoL and other clinical outcome assessments in the entire adjuvant phase.
Adjuvant analysis set for trastuzumab emtansine IV cohort	All participants with residual disease entering the trastuzumab emtansine IV arm of the adjuvant phase and receiving at least one dose of trastuzumab emtansine IV. This analysis set will be used for the analysis of HRQoL and safety in the trastuzumab emtansine IV arm.
Adjuvant cross-over modified Intention-to-Treat (mITT) analysis set	All participants randomly assigned into the cross-over period, receiving at least one PH FDC SC treatment in the cross-over period, and having a valid response to Question 1 of PPQ. This analysis set will be used for the analysis of the primary endpoint and HCPQ in the crossover period.
Adjuvant cross-over ITT analysis set	All participants randomly assigned into the cross-over period of PH FDC SC treatment, whether or not the assigned study treatment was received or a valid response to PPQ Question 1. This analysis set will be used for the analysis of the primary endpoint and HCPQ in the crossover period as a sensitivity analysis.
Adjuvant cross-over safety analysis set	All participants randomly assigned into the cross-over period and receiving at least one PH FDC SC treatment in the cross-over period. This analysis set will be used for the safety analysis in the cross-over period.

9.4 STATISTICAL ANALYSES

The Statistical Analysis Plan will be finalized prior to the first statistical analysis of study data, and it will 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. *The analyses specified in the Statistical Analysis Plan supersede those specified here.*

9.4.1 General Considerations

All data collected in this study will be analyzed in a descriptive manner. The analysis for neoadjuvant and adjuvant phases will be separated. A general rule for baseline measurement is the last available measurement before the first administration of study drug(s) for the corresponding study phase.

9.4.2 Primary Endpoint(s)

The primary endpoint is the proportion of participants who prefer PH FDC SC administered by an HCP in the home setting compared with the hospital setting during

the cross-over period of the adjuvant phase in the study, as defined in Section 3 (see Table 6).

The primary endpoint will be assessed through Question 1 of PPQ (Appendix 5). The PPQ will be completed by the participants in Arm C and D who have entered the cross-over period of the study, using a paper form provided by the Sponsor. The PPQ will be completed on Day 1 of the last cycle of the cross-over period (see Table 4). Participants who entered the cross-over period but discontinued study treatment prior to the last cycle of the cross-over period should also complete the questionnaire at the time of discontinuation as long as they have received at least one dose PH FDC SC in the home setting.

The primary endpoint will be analyzed using the adjuvant cross-over mITT analysis set (Section 9.3). A point estimate will be calculated with associated 95% Clopper–Pearson CI for the proportion of participants who prefer PH FDC SC administered by HCP in the home setting, as well as in the hospital setting. The analysis will be repeated using the adjuvant cross-over ITT analysis set as a sensitivity analysis (Section 9.3). Missing answer(s) for Question 1 of PPQ will be considered as not preferring administration in the home setting.

The primary endpoint will also be presented by stratification factors in a descriptive manner.

9.4.3 Secondary Endpoints

Analysis of secondary endpoints will be performed separately for the neoadjuvant and adjuvant phases.

The secondary endpoints for the **neoadjuvant phase** are:

- HCPQ collected for PH FDC SC or P+H IV during the neoadjuvant phase of the study
- HRQoL for participants treated with PH FDC SC or P+H IV during the neoadjuvant phase of the study
- The pCR data post-surgery
- The safety and tolerability of PH FDC SC and P+H IV during neoadjuvant phase of the study, as measured by
  - Incidence, nature and severity of all AEs, Grade ≥ 3 AEs, SAEs and cardiac AEs (including LVEF events) with severity determined according to NCI CTCAE v5.0 (Appendix 14 and Appendix 16)
  - Incidence of premature withdrawal from the neoadjuvant treatment with PH FDC SC and P+H IV
  - Targeted vital signs and physical findings
  - Targeted clinical laboratory test results

The secondary endpoints for the **adjuvant phase** are:

- HCPQ collected for PH FDC SC administration during the adjuvant cross-over period of the study
- HRQoL for participants treated with PH FDC SC during the adjuvant phase of the study
- HRQoL for participants treated with trastuzumab emtansine IV during the adjuvant phase
- *Patient's choice of setting for the treatment continuation period*
- The safety and tolerability of PH FDC SC for the cross-over period as well as the entire adjuvant phase of the study, as measured by the same safety metrics as above
- The safety and tolerability of the trastuzumab emtansine IV during the adjuvant phase of the study, as measured by the same safety metrics as above

HCPQ will be assessed by summarizing responses to individual questions by time and corresponding treatment, using corresponding analysis sets (see Section 9.3).

HRQoL, as measured by EORTC QLQ-C30 scores including change from baseline, will be summarized by time, and corresponding treatment, using corresponding analysis sets (see Section 9.3). Baseline is defined as Day 1 Cycle 1 measurement in the corresponding study phase. Comparison between the home and hospital settings in EORTC QLQ-C30 data during the cross-over period will be explored.

The proportion of participants who choose the home or the hospital administration of PH FDC SC for the treatment *continuation* period of the adjuvant phase will be reported.

The analysis of AEs will focus on treatment-emergent AEs, i.e., AEs occurring on or after the day of first study drug administration. Non-treatment emergent AEs (i.e., those occurring before start of study treatment) will be listed (with a flag to identify those AEs that continued into on-study treatment cycles). 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 AEs, Grade ≥ 3 AEs, SAEs, AESIs, AEs leading to death, and AEs leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment–emergent AEs) 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. The incidence of deaths and cause of deaths will be listed and summarized by corresponding treatment, neoadjuvant/adjuvant phase and overall.

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 (screening) and maximum post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

The ECOG performance status will be summarized via the number and percentage of participants for each combination of baseline and post-baseline ECOG scores, by treatment arm(s) in the corresponding analysis set (see Section 9.3). Baseline here refers to Day 1 Cycle 1 outcome in the corresponding study phase.

Data collected in the treatment arm of trastuzumab emtansine IV, such as HRQoL and safety, will be descriptive only.

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

Concomitant medication will be coded and tabulated in summary tables. The use of anaphylactic medications will be summarized as part of safety outcome.

9.4.3.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment and neoadjuvant/adjuvant phase. The reasons for study treatment discontinuation or study discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment.

9.4.3.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics (including but not limited to age, sex, race, ethnicity, country, early or locally advanced/inflammatory breast cancer status) will be summarized by treatment arm and neoadjuvant/adjuvant phase. Baseline data are the last data obtained prior to initiation of study treatment in the corresponding phase. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.5 INTERIM ANALYSIS

Given the exploratory nature of this study, the Sponsor may choose to conduct interim analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. If conducted, the results of this interim analysis will be evaluated by the Sponsor study core team personnel.

9.6 INDEPENDENT DATA MONITORING COMMITTEE

There is no independent Data Monitoring Committee for this study.

9.7 INTERNAL MONITORING COMMITTEE

The Sponsor's Internal Monitoring Committee (IMC) would be established to monitor and evaluate participant safety and composed of selected members representing medical, safety, and statistics functions.

The IMC will follow a charter that outlines their roles and responsibilities and ability to make recommendations regarding continuation of the study to protect the interests of the participants in this study. The IMC will be responsible for monitoring the safety of participants in the study and making recommendations regarding the conduct of the study, including study continuation as planned or with modification or early discontinuation of the study for excessive toxicity. The operating procedures are detailed in the IMC charter.

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol 2020;38:1346–66.

Andrulis IL, Bull SB, Blackstein ME, et al. for the Toronto Breast Cancer Study Group. Neu/erbB-2 amplification identifies a poor prognosis group of women with node negative breast cancer. J Clin Oncol 1998;16:1340–9.

Arteaga CL, Sliwkowski MX, Osborne CK, et al. Treatment of HER2-positive breast cancer: current status and future perspectives. Nat Rev Clin Oncol 2011:29;9:16–32.

Collins DS, Sánchez-Félix M, Badkar AV, et al. Accelerating the development of novel technologies and tools for the subcutaneous delivery of biotherapeutics. J Control Release 2020;321:475–82.

Denys H, Martinez-Mena CL, Martens MT, et al. Safety and tolerability of subcutaneous trastuzumab at home administration, results of the phase IIIb open-label BELIS study in HER2-positive early breast cancer. Breast Cancer Res Treat 2020;181:97–105.

[EMA] European Medicines Agency. An overview of Phesgo and why it is authorised in the EU. Reference EMA/620936/2020. 2020. Available at https://www.ema.europa.eu/en/documents/overview/phesgo-epar-medicine-overview_en.pdf [accessed 12 April 2021].

[FDA] Food and Drug Administration. Pathological complete response in neoadjuvant treatment of high-risk early-stage breast cancer: Use as an endpoint to support accelerated approval guidance for industry. 2020. Available at https://www.fda.gov/media/83507/download [accessed 06 December 2021].

Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. 2020; Available at https://gco.iarc.fr/today [accessed 12 April 2021].

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Gradishar WJ, Hurvitz SA, O'Regan RM, et al. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Breast Cancer. Version 2.2021 [internet]. Available at https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf [accessed 12 April 2021].

Jackisch C, Stroyakovskiy D, Pivot X, et al. Subcutaneous vs intravenous trastuzumab for patients with ERBB2-positive early breast cancer: final analysis of the HannaH phase 3 randomized clinical trial. JAMA Oncol 2019;5:e190339.

Kirschbrown WP, Wynne C, Kågedal, M et al. Development of a subcutaneous fixed-dose combination of pertuzumab and trastuzumab: results from the phase Ib dose-finding study. J Clin Pharmacol 2019;59:702–16.

Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335–7.

O'Shaughnessy J, Sousa SP, Cruz J, et al. Abstract 80O. Patient (pt) preference and satisfaction with the subcutaneous fixed-dose combination of pertuzumab (P) and trastuzumab (H) in pts with HER2-positive early breast cancer (HER2+ eBC): interim analysis of the open-label, randomised cross-over PhranceSCa study. Abstract presented at European Society for Medical Oncology (ESMO) Breast Cancer Virtual 2020. Available at https://www.annalsofoncology.org/article/S0923-7534(20)36099-3/pdf [accessed 12 April 2021].

O'Shaughnessy J, Sousa S, Cruz J, et al. PhranceSCa study group. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PhranceSCa): A randomised, open-label phase II study. Eur J Cancer. 2021;152:223–32.

Pauletti G, Dandekar S, Rong H, et al. Assessment of methods for tissue-based detection of the HER-2/neu alteration in human breast cancer: a direct comparison of fluorescence in situ hybridization and immunohistochemistry. J Clin Oncol 2000;18:3651–64.

Pivot X, Gligorov J, Müller V et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. Lancet Oncol 2013;14:962–70.

Rubin I and Yarden Y. The basic biology of HER2. Ann Oncol 2001;12 Suppl 1:S3–8.

Rummel M, Kim TM, Aversa F, et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). Ann Oncol 2017;28:836–42.

Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol 2016;34:611–35.

Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278–84.

Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177–82.

Tan AR, Im SA, Mattar A, et al. FeDeriCa study group. Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study. Lancet Oncol 2021;22:85–97.

Toikkanen S, Helin H, Isola J, et al. Prognostic significance of HER-2 oncoprotein expression in breast cancer: a 30-year follow-up. J Clin Oncol 1992;10:1044–8.

U.S. Food and Drug Administration. 2020b. FDA approves breast cancer treatment that can be administered at home by health care professional [Press release]. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-breast-cancer-treatment-can-be-administered-home-health-care-professional [accessed 12 April 2021].

U.S. Food and Drug Administration. Highlights of prescribing information. Reference ID: 4632889. 2020a. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761170s000lbl.pdf [accessed 12 April 2021].

U.S. Food and Drug Administration. Highlights of prescribing information. Reference ID: 4115233. 2017. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761064s000lbl.pdf [accessed 12 April 2021].

Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Eng J Med 2012;367:1783−91.

Walsh CA, Minnock P, Slattery C, et al. Quality of life and economic impact of switching from established infliximab therapy to adalimumab in patients with rheumatoid arthritis. Rheumatology 2007;46:1148–52.

Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. Arch Pathol Lab Med 2018;142:1364–82.

Wolfromm A, Mittaine B, Gandrille N, et al. Home administration of subcutaneous rituximab is safe and associated with significant cost saving: a single center experience. Blood 2017;130:4676.

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

TABLE OF CONTENTS

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) *E6* Guideline for Good Clinical Practice
- Applicable laws and regulations.

The protocol, Informed Consent Form, PH FDC SC, pertuzumab, and trastuzumab emtansine Investigator's Brochures, trastuzumab SmPC, 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 Trial*s* Directive (2001/20/EC) or Clinical Trials Regulations (536/2014) (EEA 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 *their* 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 *their* 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 *their* 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 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 65 sites globally will participate to enroll approximately 330 participants. Enrollment will occur through an interactive voice or web-based response system.

Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A Steering Committee will be established to provide scientific and medical guidance on the study protocol and study design, provide scientific and medical advice during the study and review any relevant study related documents or procedures to help ensure the timely collection of data that are accurate and complete, including implementation of IMC recommendations. The Steering Committee will be made up of HCPs and Sponsor representatives.

A separate Steering Committee Charter outlines the committee's composition, members' roles and responsibilities, and the frequency of meetings.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data 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/

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic 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.

A1–8 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 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.

A1–9 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. *Reasons for terminating the study may include, but are not limited to, the following:*

- *The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants*
- *Participant enrollment is unsatisfactory*

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 investigators shall promptly inform the participants and should ensure appropriate participant therapy and/or follow up.

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
Safety Parameters: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

TABLE OF CONTENTS

A2–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient 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 or clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, or are 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.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse events or serious adverse events if they fulfill the definition of an adverse event or serious adverse event. “Lack of efficacy” or “failure of expected pharmacological action” also constitutes an adverse event or serious adverse event (see Section A2–7.10).

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 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 (v 5.0) grading scale. The investigator will use the grading scale in Table 1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table 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), per the definition of serious adverse event in Section A2–2.

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 (for PH FDC SC, pertuzumab, and trastuzumab emtansine) or SmPC (for trastuzumab) 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 healthcare professionals.

If a participant dies during participation in the study, the investigator will provide the Sponsor with a copy of any post-mortem findings (if available), including histopathology (if available).

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 offline 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 offline, 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

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel and/or the mobile healthcare professional will be recorded.

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, whichever is longer, are provided in Section A2–6.

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

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as more than 28 days after the final dose of study treatment) if the event is believed to be related to prior exposure to study treatment. These events 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 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A2–7.1.1 Injection/Infusion Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion or injection should be captured as a diagnosis (e.g., "infusion-related reaction" or "injection-related reaction" or "injection-site 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 Infusion-Related Reaction and 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 as a separate event on the Adverse Event eCRF, with associated signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction and Injection Reaction eCRF.

A2–7.1.2 Other Adverse Events

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.

A2–7.2 ASYMPTOMATIC DECLINES IN LEFT VENTRICULAR EJECTION FRACTION

Asymptomatic declines in LVEF should not be reported as AEs because LVEF data are collected separately in the eCRF. 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 AE with the term of “ejection fraction decreased”, as per NCI CTCAE v5.0 (see Appendix 14 and Appendix 16). In addition, a comment in the AEs 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 AE of special interest and must be reported in an expedited manner (see A2–5). The event must be reported as an AE with the term of “ejection fraction decreased”, as per NCI CTCAE v5.0 (see Appendix 14 and Appendix 16) and a comment should be added to the AEs comments field confirming that the event was asymptomatic.

Table 2 summarizes the reporting conventions for LVSD and heart failure.

Table 2 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 on eCRF.	NA	NA
Asymptomatic decline in LVEF of ≥ 10 percentage points from baseline to an LVEF of < 50%	AE [a] (eCRF 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 (eCRF AE eForm) and report as a non-serious AEs of special interest on an SAE form	Ejection fraction decreased [a]	NCI CTCAE for "ejection fraction decreased"
Heart failure / CHF (symptomatic LVSD) [b]	AE (eCRF AE eForm) and SAE (SAE form)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA class

AE = adverse event; CHF = congestive heart failure; eCRF = electronic Case Report Form; 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. Report the status as asymptomatic and provide the LVEF value in the comments field as appropriate.

b. Any symptomatic LVSD event must be reported as "heart failure."

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 time points. 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 A2–5 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 time points 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 A2–7.3) 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 internal 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

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of breast cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated 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 the investigator’s assessment as per institutional practice. 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 *PATIENT*-REPORTED OUTCOME DATA

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

A2–8 SPECIAL SITUATIONS (ACCIDENTAL OVERDOSE AND/OR MEDICATION ERROR)

Accidental overdose and medication error (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*
- *Medication error: accidental deviation in the administration of a drug (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration)*

After initiation of study drug, special situations associated with PH FDC SC, pertuzumab, trastuzumab, and trastuzumab emtansine IV, and any associated adverse events will be reported until 28 days after the final dose of study drug.

Special situations, regardless of whether they result in an adverse event, should be reported on the Special Situations eCRF. If there are any associated adverse events, each event should be recorded separately on the Adverse Event eCRF.

Special situations and any associated adverse events should be reported within 30 days after the investigator becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as described in Section A2–5.

Appendix 3
Safety Plan: Management of Identified and Potential Risks

TABLE OF CONTENTS

Pertuzumab and trastuzumab drug substances in PH FDC SC are identical to the drug substances in pertuzumab for IV infusion and trastuzumab for IV infusion and SC injections. The safety profiles and tolerability of trastuzumab for SC injections and for IV infusions have been shown to be consistent (Roche Study BO22227).

The safety plans for this study, are based on the anticipated safety risks of PH FDC SC, as seen in the Phase III Roche Study WO40324, and trastuzumab IV/SC and pertuzumab alone and in combination, described in the PH FDC SC, pertuzumab, and trastuzumab emtansine Investigator's Brochures, and trastuzumab SmPC.

Measures taken to ensure the safety of participants in this study include eligibility criteria designed to exclude participants at higher risk for toxicities and ongoing safety monitoring. Safety monitoring includes assessment of the nature, frequency, and severity of AEs and cardiac function evaluations.

The anticipated important safety risks for PH FDC SC, pertuzumab, trastuzumab, and trastuzumab emtansine are outlined below. Please refer to the PH FDC SC, pertuzumab, and trastuzumab emtansine Investigator's Brochures, and trastuzumab SmPC, for complete summaries of safety information.

A3–1 RISKS ASSOCIATED WITH PERTUZUMAB

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

Like other monoclonal antibodies, pertuzumab has been associated with ARRs. These include:

- Infusion-related reactions (i.e., a systemic reaction with symptoms such as chills, diarrhoea, fatigue, headache, nausea and pyrexia).

  Such reactions are likely to be due to cytokine release and typically occur during, or very shortly after, the administration of monoclonal antibodies, but they may also show a delayed onset. In general, infusion-related AEs are more frequent and severe with the first infusion, and decrease in number and severity over time. The majority of AEs resolve fully.
- Injection-related reactions with SC administration may manifest themselves as:
  - Systemic reactions, similar to the infusion-related reactions
  - Local injection site reactions (ISRs) with signs and symptoms such as erythema, induration, swelling, pain, hypoesthesia and discomfort

Hypersensitivity reactions / anaphylaxis are systemic reactions caused activation of mast cells and basophils by antigen-bound IgE that results in degranulation and release of inflammatory mediators. Hypersensitivity reactions / anaphylaxis events are likely to start mildly and increase in number and severity over time. Severe hypersensitivity, including anaphylaxis, has been observed in clinical trials with treatment of pertuzumab. Participants in this study who experience a Grade 4 allergic reaction or acute respiratory distress syndrome (ARDS) should be discontinued from study treatment. Since there is a potential for delayed onset, participants should be instructed to contact the treating physician with any concerns, signs or symptoms subsequent to treatment administration. Administration-related reactions may be difficult to distinguish from hypersensitivity reactions.

In this study, a loading dose of pertuzumab will be given over 60 (± 10) minutes, followed by an observation period of 60 minutes. If the loading dose infusion is well tolerated, subsequent infusions may be administered over a period of 30 minutes (± 10) with an observation period of 30 minutes. If symptoms occur, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. The observation period should be completed prior to the subsequent trastuzumab IV infusion. Pre-medication with antipyretics, antihistamines, or corticosteroids may be administered before pertuzumab administration.

Pertuzumab will be administered by staff who have immediate access to emergency equipment and are trained to monitor for, and respond to, medical emergencies.

Please refer to the pertuzumab Investigator's Brochure for the most recent data related to the risk of hypersensitivity reactions.

A3–1.2 SYMPTOMATIC LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Similar to trastuzumab, pertuzumab's interaction with HER2 may be associated with a risk of symptomatic LVSD. Cardiac dysfunction may manifest as an asymptomatic or mildly symptomatic decrease in LVEF (NCI CTCAE, Grade 1 and Grade 2) or as a symptomatic decreased in LVEF / CHF (NCI CTCAE, Grade ≥ 3; NYHA Class III or IV). Please refer to Appendix 16 for management of participants with decreased LVEF.

In the Roche pivotal trial WO20698/TOC4129g (CLEOPATRA) in metastatic breast cancer patients, treatment with P+H IV and docetaxel was not associated with increases in the incidence of symptomatic LVSD or LVEF declines compared with placebo in combination with trastuzumab IV and docetaxel. The incidence of symptomatic LVSD was 1.5% (6/408) for participants receiving P+H IV and docetaxel (events in the treatment period only) and 1.5% (7/396) in the placebo arm. Regardless of treatment arm, participants who had received prior anthracyclines or prior radiotherapy to the chest area were at higher risk of decreased LVEF. In the Roche Phase II WO209697 study (NEOSPHERE) of neoadjuvant P+H IV and docetaxel, the incidence of left ventricular dysfunction defined as LVEF decline ≥ 10% to below 50% was higher in the pertuzumab plus docetaxel-treated groups (7.4% with pertuzumab plus docetaxel, 8.4% P+H IV plus docetaxel) than the trastuzumab IV plus docetaxel treated group (1.9%). An increased incidence of LVEF declines was observed in participants treated in the pertuzumab plus trastuzumab IV and docetaxel. Left ventricular ejection fraction recovered to ≥ 50% in all participants. In the ongoing Roche Phase II WO29217 study (BERENICE; neoadjuvant anthracycline / taxane based regimens given in combination with P+H IV), the overall incidence of LVEF declines and symptomatic LVD in the neoadjuvant period is consistent with previous data in the neoadjuvant setting.

Pertuzumab has not been studied in patients with the following: a pre-treatment LVEF value of ≤ 50%; a prior history of CHF; decreases in LVEF to < 50% during prior trastuzumab adjuvant therapy; conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment, or a cumulative prior anthracycline exposure to > 360 mg/m^2 of doxorubicin or its equivalent.

Subjects with significant cardiac disease or baseline LVEF < 55% are not eligible for this study. As in all pertuzumab trials, study participants must undergo routine cardiac monitoring by ECHO or MUGA scan. During the screening / baseline period, complete medical history information will be collected from all participants to explore possible risk factors for treatment-associated CHF. Monitoring of LVEF is required while participants

are receiving study treatment and during the follow-up period following discontinuation of study treatment (see Section 1.3). If symptomatic LVSD (heart failure; SAE of NCI CTCAE v4.0 Grade 3 or 4; NYHA Class III or IV) 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 algorithm in Appendix 16 for decisions regarding the continuation or discontinuation of study treatment based on LVEF assessment in asymptomatic participants.

Please refer to the pertuzumab Investigator's Brochure for the most recent data relating to risk of LVSD and CHF.

A3–1.3 EPIDERMAL GROWTH FACTOR RECEPTOR (HER1)-RELATED TOXICITIES

Pertuzumab inhibits HER2 heterodimerization with other members of the HER family including HER1/EGFR. As a result, pertuzumab may cause toxicities associated with the use of EGFR tyrosine kinase inhibitors such as diarrhea, rash and other dermatologic toxicities (e.g., dry skin, pruritus, nail disorders, mucositis).

The most recent data relating to the risk of EGFR-related toxicities are found in the pertuzumab Investigator's Brochure.

A3–1.4 DIARRHEA

Diarrhea has been observed in approximately 60% of patients (treatment-related diarrhea in 50% of patients) being treated with pertuzumab in Phase II single-agent studies, and in up to 90% of participants in combination therapy studies. Diarrhea was NCI CTCAE Grade 1 or 2 in the majority of cases. To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication should be considered and participants treated with fluids and electrolyte replacement, as clinically indicated.

A3–1.5 RASH / SKIN REACTIONS

Rash / skin reactions have been observed in approximately 17% of patients treated with pertuzumab in the Phase II single-agent studies and in up to 73% of patients in combination studies. The rash was generally mild to moderate in intensity and NCI CTCAE Grade 1 or 2.

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

A3–1.6 MUCOSITIS

Mucositis has been observed in approximately 15% of patients treated with pertuzumab in Phase II single-agent studies and in up to 50% of patients in combination studies. The most common preferred terms reported were mucosal inflammation and stomatitis.

A3–1.7 INTERSTITIAL LUNG DISEASE

Interstitial lung disease is associated with the use of EGFR inhibitors and therefore could occur with pertuzumab. The few reports of interstitial lung disease in pertuzumab-treated patients received to date also had evidence of alternative causes (e.g., concomitant medication, preceding / concurrent neutropenia with potential infection or other relevant medical history).

In the pivotal study WO20698/TOC4129g (CLEOPATRA; trastuzumab IV and docetaxel with pertuzumab or placebo), respiratory events (i.e., dyspnea, cough), which are unspecific symptoms of various conditions, including infusion-related reaction or hypersensitivity / anaphylaxis, cardiac dysfunction, and respiratory disease, were reported in > 10% of pertuzumab-treated patients.

A3–2 RISKS ASSOCIATED WITH TRASTUZUMAB

Serious adverse reactions, including LVSD, ARRs, hypersensitivity, allergic-like reactions, and pulmonary events, have been observed in patients receiving trastuzumab IV and/or SC.

A3–2.1 ADMINISTRATION-RELATED REACTIONS, ALLERGIC-LIKE REACTIONS, AND HYPERSENSITIVITY

Trastuzumab IV and SC have been associated with ARRs. ARRs are defined as systemic ‘infusion-related reactions’ associated with trastuzumab IV and systemic reactions associated with trastuzumab SC. In some studies, local ISRs were excluded from the ARR definitions. A revised definition of ARRs potentially associated with IV and SC administration of trastuzumab was used in Study BO22227 and is applicable to all future and ongoing trastuzumab IV and SC studies. This definition is based on a modified version of the anaphylactic reaction Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (as modified by the addition of the following four MedDRA Preferred Terms: hypersensitivity, drug hypersensitivity, infusion-related reaction, and injection-site hypersensitivity). The revised definition of ARRs differs from that in previous studies in the metastatic and early breast cancer settings which reported only ‘infusion reactions’ or ‘infusion-related reactions’ associated with trastuzumab administration and makes comparison of the rates of ARRs between studies difficult.

Serious adverse reactions to trastuzumab IV that have been reported infrequently include dyspnea, hypotension, wheezing, bronchospasm, asthma, tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, and angioedema. Fatalities have occurred within hours and up to one week following trastuzumab IV administration. On very rare occasions, patients have experienced the onset of administration-related symptoms or pulmonary symptoms more than six hours after the start of the trastuzumab administration. Patients should be warned of the possibility of

such a late onset and should be instructed to contact their physician if these symptoms occur. Patients who have dyspnea at rest due to comorbidities may be at increased risk of a fatal ARR therefore should not be treated with trastuzumab. Although such events were not reported in clinical trials with trastuzumab SC, caution should be exercised, as these events have been associated with the IV formulation.

These reactions were usually associated with the first administration of trastuzumab IV and generally occurred during or immediately following administration. In this study a loading dose of trastuzumab IV is required. The loading dose must be administered over 90 (± 10) minutes, after which the patient must be observed for 60 minutes. If the loading dose infusion is well tolerated, subsequent maintenance doses may be administered over 30 (± 10) minutes, followed by an observation period of 30 minutes.

In Study BO22227, the overall incidence of ARRs in the trastuzumab IV arm was 37.2% (111/298) compared with 47.8% (142/297) in the trastuzumab SC arm. Most of the ARRs occurred in the neoadjuvant treatment phase, with an incidence of 32.6% in the trastuzumab IV arm and 38.4% in the trastuzumab SC arm. Fewer ARRs were reported during the adjuvant treatment phase of the study. All but one of the ARRs was Grade 1 or Grade 2 in intensity and the distribution was balanced between the study phases in terms of the most common AEs and MedDRA System Organ Class. There was a higher rate of trastuzumab SC injection-site reactions compared with the trastuzumab IV infusion (11.1% in trastuzumab SC vs. 0.3% in trastuzumab IV). With few exceptions, all of these events were of Grade 1 intensity. Serious reactions to trastuzumab IV have been treated successfully with supportive therapy, such as oxygen, β-agonists, and corticosteroids.

In this study, patients should be monitored for 60 minutes after their first pertuzumab and trastuzumab IV dose administration. Patients should be monitored for 30 minutes following subsequent administrations unless a loading dose is required. If ARRs occur, patients must be monitored until complete resolution of signs and symptoms.

Trastuzumab IV will be administered by staff with immediate access to emergency equipment who are trained to monitor for, and respond to, medical emergencies.

Please refer to the trastuzumab SmPC for the most recent data related to the risk of ARRs, allergic-like reactions, and hypersensitivity reactions.

A3–2.2 PULMONARY EVENTS

Severe pulmonary events have been reported with the use of the trastuzumab IV formulation in the post-marketing setting. These events have occasionally been fatal. They may occur as part of an ARR or with delayed onset. In addition, cases of interstitial lung disease, including lung infiltrates, ARDS, pneumonia, pneumonitis, pleural effusion,

respiratory distress, acute pulmonary edema, and respiratory insufficiency have been reported with trastuzumab IV. These events have been most common with the first infusion, and their severity has decreased with subsequent infusions. Serious reactions have been treated successfully with supportive therapy, such as oxygen, β-agonists, and corticosteroids. Acute respiratory distress syndrome has been reported with a fatal outcome.

Please refer to the trastuzumab SmPC for the most recent data related to the risk of pulmonary events.

A3–2.3 SYMPTOMATIC LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Heart failure (NYHA Class II - IV) has been observed in patients who have received trastuzumab IV and/or SC alone or in combination with docetaxel following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This event may be moderate to severe and has been associated with death. Risk factors for trastuzumab-associated LVSD include increased age, concomitant administration with anthracyclines, and declining LVEF while on trastuzumab treatment. If symptomatic cardiac failure develops during treatment, it should be treated with standard medications for this purpose.

The rates of cardiac dysfunction observed in large trastuzumab adjuvant trials in EBC are < 4% with event rates comparable across the studies. In Study BO22227, the proportion of patients who experienced a significant decrease in LVEF (defined as a drop in LVEF ≥ 10 percentage points to a value of < 50%) was similar in each treatment arm (12 [4.2%] patients in trastuzumab IV and 11 [3.8%] patients in trastuzumab SC).

Because the half-life of trastuzumab IV is approximately 28–38 days, trastuzumab may persist in the circulation for up to 7 months after the last dose of trastuzumab. Patients who receive anthracyclines after the last dose of trastuzumab may possibly be at increased risk of LVSD. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks (7 months) after stopping trastuzumab. If anthracyclines are used, the patient’s cardiac function should be monitored carefully.

Most patients who developed heart failure in the Phase III trials of trastuzumab IV or SC in metastatic breast cancer and early breast cancer improved with standard medical treatment. This treatment included diuretics, cardiac glycosides, and/or ACE inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on weekly therapy with trastuzumab without experiencing additional clinical cardiac events.

Please refer to the trastuzumab SmPC for the most recent data related to the risk of LVSD.

A3–3 RISKS ASSOCIATED WITH PH FDC SC

A3–3.1 HYPERSENSITIVITY REACTIONS / ANAPHYLAXIS AND ADMINISTRATION-RELATED REACTIONS

In the Phase III Roche Study WO40324 (FeDeriCa), administration-related reactions (ARR) AEs occurring within 24 hours of HER2-targeted therapy were slightly higher in the PH FDC SC arm (43 [17.3%] participants) compared to the P+H IV arm (34 [13.5%] participants) and were of low Grade for the majority. Three participants in the P+H IV arm and none in the PH FDC SC arm experienced Grade 3 events.

The most frequently reported preferred terms (PTs) (in ≥5% of cases) included injection site reaction: one (0.4%) in the P+H IV (in a participant who switched to trastuzumab SC during the adjuvant treatment period) vs. 32 (12.9%) participants in the PH FDC SC arm; and infusion-related reaction: 25 (9.9%) participants in the P+H IV vs. 0 (0%) participants in the PH FDC SC arm. The injection site reactions, related to the SC route of administration of PH FDC SC, are the main reason for the observed numerical imbalance of ARRs.

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

Overall, hypersensitivity and anaphylaxis events occurred with low and comparable incidence across the treatment arms (five [2.0%] participants in the P+H IV arm vs. four [1.6%] participants in the PH FDC SC arm). Except for one event (Grade 3 hypersensitivity related to a concomitant medication at study Cycle 4), all events occurred after study Cycle 5 and were related to HER2-targeted therapy (four [1.6%] participants in each arm). The reported events by PT were injection-related reaction, hypersensitivity, and drug hypersensitivity. All events related to HER2-targeted therapy 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 AEs related to HER2 reported during or within 24 hours of administration were low in both arms (two [0.8%] participants in the P+H IV arm vs. two [0.8%] participants in the PH FDC SC arm), 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

patients treated with PH FDC SC, caution should be exercised as these have been associated with intravenous pertuzumab in combination with trastuzumab and chemotherapy.

For PH FDC SC administration, participants should be monitored for at least 30 minutes after their first dose regardless of whether a loading dose is required. Participants should be monitored for at least 15 minutes following subsequent administrations unless a loading dose is required. If a participant requires a loading dose after their first PH FDC SC treatment, they should be monitored for at least 30 minutes after dosing. If ARRs occur, participants must be monitored until complete resolution of signs and symptoms.

PH FDC SC will be administered by staff who have immediate access to emergency equipment and are trained to monitor for, and respond to, medical emergencies. An anaphylaxis kit will be provided by the Sponsor (See Section 6.1.6).

Participants who experience an NCI-CTCAE version 5.0 Grade 4 allergic reaction, acute respiratory distress syndrome (ARDS), or bronchospasm will be discontinued from study treatment.

Pre-medication with corticosteroids, antihistamines, and antipyretics may be used before subsequent PH FDC SC injections at the investigator's discretion. If injection associated symptoms occur, participants will be monitored until complete resolution of signs and symptoms

Please refer to the PH FDC SC and pertuzumab Investigator's Brochures, and the trastuzumab SmPC, for the most recent data related to the risk of hypersensitivity reactions.

A3–3.2 LEFT VENTRICULAR DYSFUNCTION

In the Phase III Roche Study WO40324 (FeDeriCa), 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 P+H IV arm and two (0.8%) participants in the PH FDC SC arm who met the criteria for a primary cardiac event: one (0.4%) participant had heart failure with LVEF drop of at least 10 percentage points from baseline and to below 50%, and one (0.4%) participant with cardiac death.

The event of heart failure was reported in an elderly participant in the PH FDC SC arm. The onset of the AE occurred 18 days after Cycle 4 Day 1 of doxorubicin (Adriamycin®) plus cyclophosphamide (AC) (Q3W) and became serious 12 days after Cycle 6 Day 1 of PH FDC SC. 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 PH FDC SC treatment and had resolved at the time of the clinical cut-off date.

The event of cardiac death was reported in an elderly participant in the PH FDC SC arm. The event was due to an acute myocardial infarction which occurred after Cycle 2 of dose-dense doxorubicin (Adriamycin®) 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 AE reporting (ejection fraction decreased) and under LVEF assessment.

Overall, nine (3.6%) participants in the P+H IV arm vs. four (1.6%) participants in the PH FDC SC arm, had at least one LVEF decrease of 10 percentage points below the baseline measurement to an absolute LVEF value of < 50%. Of these, the initial LVEF decline was confirmed by a second LVEF assessment for two (0.8%) participants in the P+H IV arm and one (0.4%) participant in the PH FDC SC arm; hence overall, three 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 percentage points below the baseline measurement to an absolute LVEF value of < 50% during study were:

- Four (1.6%) and one (0.4%) events in the P+H IV arm and PH FDC SC arm, respectively, which occurred during the neoadjuvant phase
- Four (1.6%) and three (1.2%) events in the P+H IV arm and PH FDC SC arm, respectively, which occurred during the adjuvant phase

- Three (1.2%) and one (0.4%) events in the P+H IV arm and PH FDC SC arm, respectively, which occurred during the follow-up phase

Participants with significant cardiac disease or baseline LVEF < 50% are not eligible for this study. As in all pertuzumab trials, study participants must undergo routine cardiac monitoring by ECHO or MUGA scan. During the screening / baseline period, complete medical history information will be collected from all participants to explore possible risk factors for treatment-associated CHF. Monitoring of LVEF is required while participants are receiving study treatment (see Appendix 16). If symptomatic LVSD (heart failure; SAE of NCI CTCAE v5.0 Grade 3 or 4; NYHA Class III or IV) 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 algorithm in Appendix 16 for decisions regarding the continuation or discontinuation of study treatment based on LVEF assessment in asymptomatic participants.

Please refer to the PH FDC SC and pertuzumab Investigator's Brochures, and the trastuzumab SmPC, for the most recent data relating to risk of LVSD and CHF.

Left ventricular function will be monitored by measurement of ejection fraction using echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans as described in Section 8.2. and the schedule of activities (see Section 1.3).

A3–3.3 DIARRHEA

In the Phase III Roche Study WO40324 (FeDeriCa), the incidence and severity of diarrhea events were comparable between the two treatment arms (55.2% of participants in the P+H IV arm vs. 58.5% of participants in the PH FDC SC arm). 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%] participants in the P+H IV arm vs. 17 [6.9%] participants in the PH FDC SC arm). There was one Grade 4 event in the P+H 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% of participants in the P+H IV arm vs. 30.6% of participants in the PH FDC SC arm). Grade 3–4 diarrhea events related to HER2 were reported in five (2.0%) participants in the P+H IV arm vs. nine (3.6%) participants in the PH FDC SC arm. No events of diarrhea led to withdrawal of HER2-targeted therapy.

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.

A3–3.4 RASH / SKIN REACTIONS

In the Phase III Roche Study WO40324 (FeDeriCa), there was only one event of serious rash/skin reaction in the PH FDC SC 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.

A3–3.5 INTERSTITIAL LUNG DISEASE

In the Phase III Roche Study WO40324 (FeDeriCa) incidence of interstitial lung disease (ILD) AEs was low and balanced between the two treatment arms (two [0.8%] participants in the P+H IV arm vs. three [1.2%] participants in the PH FDC SC arm). Both events in the P+H IV arm occurred prior to HER2-targeted therapy and were assessed as related to chemotherapy.

In the PH FDC SC arm, SAEs were reported in one (0.4%) and two (0.8%) participants with ILD which were assessed by the investigator as related to doxorubicin plus cyclophosphamide chemotherapy and HER2-targeted therapy, respectively. All events were Grade 2 and had resolved by the time of clinical cut-off date.

A3–4 REPRODUCTIVE TOXICITY ASSOCIATED WITH PERTUZUMAB AND TRASTUZUMAB

Reproductive toxicity was identified during nonclinical studies with pertuzumab. Pertuzumab administered to pregnant cynomolgus monkeys during organogenesis led to delayed renal development, oligohydramnios, and embryo-fetal 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. 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 trastuzumab. Therefore, neither pertuzumab or trastuzumab should be used during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

Due to these risks, female participants of childbearing potential in this study are tested for pregnancy prior to study entry and must undergo pregnancy testing during the study and, up to 7 months after their last study treatment. Pregnancies in female participants or partners of male participants will be monitored. Further, participants of childbearing potential (defined as post-menarchal, has not reached a post-menopausal state [post-menopausal defined as ≥ 12 continuous months of amenorrhea with no identified cause other than menopause], and has not undergone surgical sterilization [removal of ovaries and/or uterus]), must remain abstinent (refrain from heterosexual intercourse) or use

contraceptive methods with a failure rate of <1% per year, or two effective contraceptive methods during the study treatment periods and for 7 months after the last dose of study treatment and must refrain from donating eggs during the same period. Women who have had a tubal ligation do not require additional contraception. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

Men with female partners of childbearing potential, or with pregnant female partners, participating in the study must remain abstinent or use a condom during the study treatment periods and for seven months after the last dose of study treatment to avoid exposing the embryo. All male participants must also refrain from donating sperm during this same period.

A3–4.1 BREASTFEEDING TOXICITY

It is not known whether trastuzumab or pertuzumab are excreted in human milk. Since maternal IgG is excreted in milk and either trastuzumab or pertuzumab could harm infant growth and development, women must discontinue nursing during study treatment and should not breastfeed for at least seven months following the last study treatment.

A3–5 INFECTION DURING COVID-19 PANDEMIC

This study may place vulnerable patient populations at increased risk, including those with cancer, among other comorbidities (Liang et al. 2020). There is currently limited clinical data available for COVID-19 and there is currently no data on the use of pertuzumab and trastuzumab in patients diagnosed with COVID-19.

Individuals with any severe infection within 28 days prior to initiation of study treatment will be excluded. Participants will be assessed for COVID-19 at screening and during study if indicated.

For participants with fever or other symptoms of infection (cough, difficulty breathing):

- Participants must be advised to immediately contact the investigator
- A comprehensive evaluation should be performed as per usual medical practice and institutional guidelines
- If the diagnosis of COVID-19 is confirmed the prescriber should follow standard clinical management plans and start the study treatment after the COVID-19 is resolved.

See Appendix 17 for COVID-19-related safety reporting instructions.

A3–6 RISKS ASSOCIATED WITH TRASTUZUMAB EMTANSINE

A3–6.1 PULMONARY TOXICITY

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical trials with trastuzumab emtansine. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates.

It is recommended that treatment with trastuzumab emtansine be permanently discontinued in patients who are diagnosed with ILD or pneumonitis of ≥ Grade 2, except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for ≥ Grade 3 or for Grade 2 not responding to standard treatment. For pneumonitis of Grade 1 that is not induced by radiation, trastuzumab emtansine should be withheld until resolution of the event; once resolved, treatment with one dose level reduction may proceed.

Patients with dyspnea at rest due to complications of advanced malignancy, comorbidities and receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary events.

Guidelines for management of trastuzumab emtansine in patients who develop ILD or pneumonitis are provided in Section A3–9.2.

A3–6.2 HEPATOTOXICITY

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1 – 4 transaminitis), has been observed while on treatment with trastuzumab emtansine in clinical trials. Transaminase elevations were generally transient with peak elevation at day 8 after therapy and subsequent recovery to Grade 1 or less prior to the next cycle. A cumulative effect of trastuzumab emtansine on transaminases has also been observed. Patients with elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of trastuzumab emtansine in the majority of the cases. Serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver and some with a fatal outcome due to drug-induced liver injury have been observed in patients treated with trastuzumab emtansine in clinical trials. Some of the observed cases may have been confounded by comorbidities and/or concomitant medications with known hepatotoxic potential.

Liver function should be monitored prior to initiation of treatment and each trastuzumab emtansine dose.

Trastuzumab emtansine has not been studied in patients with serum transaminases >2.5 x upper limit of normal (ULN) or total bilirubin >1.5 x ULN prior to initiation of treatment. Trastuzumab emtansine treatment in patients with serum transaminases >3 x ULN and concurrent total bilirubin >2 x ULN should be permanently discontinued.

Cases of NRH of the liver have been identified from liver biopsies in patients treated with trastuzumab emtansine. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension. NRH should be considered in all patients with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on the computed tomography (CT) scan of the liver, but with normal transaminases and no manifestations of cirrhosis. Signs and symptoms of portal hypertension may include ascites, hepatic encephalopathy, esophageal or gastric varices. All of these would require the patient to seek medical attention. Diagnosis of NRH requires histological confirmation. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued.

Patients must meet specified hepatic laboratory test requirements to be included in this study (Section 5.2.1).

Hepatic laboratory parameters will be monitored as described in the schedule of activities (Section 1.3).

Guidelines for management of trastuzumab emtansine in patients who develop increased serum transaminases, increased serum bilirubin, or NRH are provided in Section A3–9.2.

A3–6.3 LEFT VENTRICULAR DYSFUNCTION

Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction $\leq 40\%$ has been observed in patients treated with trastuzumab emtansine and therefore symptomatic CHF is a potential risk. Symptoms may include shortness of breath at rest, chest pain, peripheral edema, or tachycardia.

Risk factors include previous anthracycline therapy, prior or concurrent exposure to taxanes, patients over the age of 50 years, prior or concurrent anti-hypertensive medication use and low LVEF levels prior to or following the use of paclitaxel. In contrast to anthracycline-induced cardiac toxicity, trastuzumab-related cardiac dysfunction does not appear to increase with cumulative dose or to be associated with ultrastructural changes in the myocardium and is generally reversible.

Patients must meet specified LVEF requirements to be included in this study (Section 5.1).

Left ventricular function will be monitored by measurement of ejection fraction using ECHO) or MUGA scans as described in Section 8.2.4 and the schedule of activities (Section 1.3).

Guidelines for patient monitoring and management of trastuzumab emtansine in patients who develop left ventricular dysfunction are provided in Section A3–9.2.

A3–6.4 INFUSION-RELATED REACTIONS AND HYPERSENSITIVITY REACTIONS

Infusion-related reactions (IRRs) and hypersensitivity reactions have been reported with administration of trastuzumab emtansine. Despite the different pathophysiology of IRRs (reactions involving cytokine release) and hypersensitivity (allergic) reactions, the clinical manifestations are the same. In general, IRRs are expected to be more frequent and severe with the first infusion and to decrease in number and severity over time. The severity of true hypersensitivity reactions would be expected to increase with subsequent infusions.

Infusion-related reactions, characterized by one or more of the following symptoms—flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia—have been reported in clinical trials of trastuzumab emtansine. In general, these symptoms were not severe. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated.

Hypersensitivity reactions, including serious anaphylactic-like reactions, have been observed in clinical trials of trastuzumab emtansine. Patients with a history of intolerance to trastuzumab will be excluded from this study (Section 5.2.1).

Administration of trastuzumab emtansine will be performed in a setting with access to emergency facilities and staff who are trained to monitor and respond to medical emergencies. Patients should be closely monitored for IRRs during and after each infusion of study treatment, as described in Section A3–9.2.

Guidelines for management of patients who experience IRRs or hypersensitivity reactions are provided in Section A3–9.2.

A3–6.5 HEMATOLOGIC TOXICITY

Thrombocytopenia *has been* reported in patients *enrolled* in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events (*platelet count*

≥50,000/μL), with the nadir occurring by *Day* 8 and generally improving to Grade ≤1 (*platelet count* ≥75,000/μL) by the next scheduled dose *(i.e., within 3 weeks)*. *Evaluation of this safety parameter across various clinical studies has shown a higher* incidence and severity of thrombocytopenia in Asian patients.

Patients with thrombocytopenia (≤100,000/μL) and patients on anti-coagulant treatment should be monitored closely *during* treatment with trastuzumab emtansine. It is *required* that platelet counts are monitored prior to each trastuzumab emtansine dose. Rare cases of severe prolonged thrombocytopenia *defined as persisting* (≥ Grade 3 thrombocytopenia *events* lasting for more than 90 days) have been reported with trastuzumab *based on cumulative data review*. In most of these cases, patients received concomitant recombinant human thrombopoietin (rhTPO). Trastuzumab emtansine has not been studied in patients with platelet counts ≤100,000/μL prior to initiation of treatment. In the event of decreased platelet count to Grade ≥3 (<50,000/μL), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 (≥75,000/μL).

Declines in other hematopoietic lineages, for example, leukopenia, neutropenia, and anemia, were less frequent than that observed for platelets.

Patients must meet specified hematologic laboratory test requirements to be included in this study (Section 5.2.1).

Hematologic laboratory parameters will be monitored as described in Section 8.2.8 and Appendix 11 and the schedule of activities (Section 1.3). Patients will require monitoring of platelets prior to each dose of trastuzumab emtansine. Patients on anticoagulant or antiplatelet treatment should be monitored closely.

Guidelines for management of trastuzumab emtansine in patients who develop hematologic toxicity are provided in Section A3–9.2.

A3–6.6 HEMORRHAGE

Cases of hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported with trastuzumab emtansine. Some of these bleeding events resulted in fatal outcomes. In some of the observed cases, the patients were also receiving anti-coagulation therapy, antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Caution should be used with these agents, and additional monitoring should be considered when concomitant use with trastuzumab emtansine is medically necessary.

A3–6.7 NEUROTOXICITY

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine. The most common symptoms of peripheral neuropathy include parasthesia or hypoesthesia.

Patients with Grade ≥3 peripheral neuropathy will be excluded from joining Arm E of this study (Section 5.2.3).

Patients will be clinically monitored on an ongoing basis for signs or symptoms of peripheral neuropathy as described in Section 8.2.1 and the schedule of activities (Section 1.3).

Guidelines for management of trastuzumab emtansine in patients who develop peripheral neuropathy are provided in Section A3–9.2.

A3–6.8 EXTRAVASATION

In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. These reactions have been observed more frequently within 24 hours of infusion. In the post marketing setting, very rare cases of epidermal injury or necrosis following extravasation have been observed. Specific treatment for trastuzumab emtansine extravasation is unknown at this time. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration, as described in Section 6.1.3.

Patients should be managed symptomatically per local institutional guidelines.

A3–7 RISKS ASSOCIATED WITH CHEMOTHERAPY DRUGS, HORMONE THERAPY, AND RADIOTHERAPY

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the currently approved prescribing information for carboplatin, doxorubicin, cyclophosphamide, docetaxel, paclitaxel, anti-estrogen therapy and radiotherapy.

A3–8 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS DURING TREATMENT WITH PH FDC SC AND P+H IV

A3–8.1 DOSE MODIFICATIONS

Dose modification of PH FDC SC or P+H IV is not permitted.

A3–8.2 TREATMENT INTERRUPTION

The administration of PH FDC SC or P+H IV may be delayed to assess or treat AEs, such as cardiac AEs.

During the study treatment period, a dose delay of up to (and including) 6 weeks (i.e., up to and including nine weeks between doses) will be permitted to allow AE recovery to baseline. Following a dose delay of less than 3 weeks (i.e., < 6 weeks between doses), study treatment does not need to be reloaded (only the maintenance doses need to be given).

Participants receiving pertuzumab plus trastuzumab (either PH FDC SC or P+H IV) with ≥ 6 weeks since their last P+H IV infusions or PH FDC SC treatment must receive a loading dose consisting (of PH FDC SC or P+H IV, as applicable) before continuing with maintenance doses for subsequent administrations.

Participants should be monitored for 30 minutes after their first PH FDC SC dose administration in the study and if another loading dose is required. Participants should be monitored for 15 minutes following subsequent PH FDC SC maintenance dose administrations.

Participants should be monitored for 60 minutes after their first P+H IV dose administration in the study and if another loading dose is required. Participants should be monitored for 30 minutes following subsequent P+H maintenance dose administrations.

Participants can be observed for longer periods at the discretion of the HCP or, if necessary, as per local requirements.

If study treatment is withheld for more than two cycles (> 9 weeks) because of toxicity, the participant should be discontinued from study treatment, unless resumption of treatment is approved by the investigator following consultation with the Medical Monitor. Study treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) at the investigator's discretion following consultation with the Medical Monitor. The investigator may consult the Medical Monitor to determine the acceptable length of treatment interruption.

Participants who are permanently discontinued from study treatment should be treated at the discretion of the investigator as clinically indicated. The participant will continue to be followed post-treatment as described in Section 7.

A3–8.3 MANAGEMENT GUIDELINES FOR PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS DURING TREATMENT WITH PH FDC SC AND P+H IV

Supportive care and medical management of AEs are at the discretion of the investigator, unless specifically listed below. Guidelines for management of specific adverse events are provided in the subsections below.

Symptomatic LVSD and/or LVEF Decline

All participants must have a baseline LVEF ≥ 55%. LVEF will be monitored regularly according to the Schedule of Activities (see Table 1 [neoadjuvant phase, treatment option 1], Table 2 [neoadjuvant phase, treatment option 2], Table 4 [neoadjuvant phase, treatment option 3], Table 4 [adjuvant phase*, Arm C and D*]*, and Table 5 [adjuvant phase, Arm E]*). If an investigator is concerned that an AE may be related to LVSD, an additional LVEF measurement should be performed as soon as possible and within 3 weeks. Symptomatic LVSD (CHF) should be assessed as "heart failure" on the basis of NCI CTCAE v5.0 and NYHA classification (see Appendix 16 and Appendix 14). Symptomatic LVSD (CHF) should be treated and monitored according to standard medical practice. These participants should be evaluated by a certified cardiologist locally.

Appendix 16 summarizes the management of study medication in participants who develop an asymptomatic decrease in LVEF. The decision to initiate study treatment and whether to continue or stop therapy 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 also showing a significant decrease.

Heart failure and asymptomatic LVEF decline AEs must be graded per NCI CTCAE v5.0 (see Appendix 16) and reported in the eCRF as described in Appendix 2.

Management: Hypersensitivity / Anaphylaxis and Administration-Related Reactions

Participants should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in patients treated with PH FDC SC, caution should be exercised as these have been associated with pertuzumab for IV infusions in combination with trastuzumab for IV infusions and chemotherapy.

Study treatment administration should be stopped in subjects 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:

- Grade 4 allergic reaction
- Grade 3 or 4 hypersensitivity reaction
- ARDS
- Bronchospasm

Participants who experience ARRs may be managed by:

- Stopping the injection of PH FDC SC or infusion of P+H IV
- Supportive care with antihistamines, antipyretics, corticosteroids or epinephrine as clinically indicated
- Subsequently pre-medicating with analgesia and antihistamines as per institutional practice

Vital signs will be monitored as described Section 8.2.2. 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 AEs must be documented with the date and time of the onset and duration of the event (i.e., resolution of the event).

EGFR-Related Toxicities

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.

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.

A3–9 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS DURING TREATMENT WITH TRASTUZUMAB EMTANSINE

A3–9.1 DOSE MODIFICATIONS AND INTERRUPTIONS

Management of symptomatic adverse events may require temporary interruption, dose reduction, or treatment discontinuation of trastuzumab emtansine IV as per guidelines provided in local label (and described in Section 6.1.3). Trastuzumab emtansine IV dose should not be re-escalated after a dose reduction is made.

A3–9.2 MANAGEMENT GUIDELINES FOR PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS DURING TREATMENT WITH TRASTUZUMAB EMTANSINE

Supportive care and medical management of AEs are at the discretion of the investigator, unless specifically listed below. Guidelines for management of specific adverse events are provided in the subsections below.

Pulmonary Events

Participants who have experienced a pulmonary event should be carefully evaluated before commencing trastuzumab emtansine treatment. It is recommended that treatment with trastuzumab emtansine be permanently discontinued in participants who are diagnosed with *ILD or pneumonitis of ≥ Grade 2, except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for ≥ Grade 3 or for Grade 2 not responding to standard treatment. For pneumonitis of Grade 1 that is not induced by radiation, trastuzumab emtansine should be withheld until resolution of the event; once resolved, treatment with one dose level reduction may proceed.*

Hepatic Events

Hepatic events observed were predominantly asymptomatic increases in serum transaminases. Participants are required to undergo frequent monitoring of liver function (prior to receiving each dose) to determine eligibility to continue treatment and to prevent more severe events.

See Table 1 for management guidelines for increased transaminases (AST/ALT) and hepatic events. See Table 2 for dose modifications of trastuzumab emtansine for hyperbilirubinemia.

Table 1 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events

Severity	Action to Be Taken
ALT or AST increase that meets Hy's law criteria: ALT or AST $>3\times$ ULN in combination with TBILI $>2\times$ ULN or clinical jaundice	Discontinue trastuzumab emtansine treatment.
ALT or AST increase that does not meet Hy's law criteria ALT/AST Grade 1 ($>$ 1-0–3.0 $\times$ ULN)	Treat at the same dose level.
ALT/AST Grade 2 (>3.0–$5.0\times$ ULN)	Treat at the same dose level.
ALT/AST Grade 3 (>5.0–$20.0\times$ ULN)	Withhold trastuzumab emtansine dose. Do not administer trastuzumab emtansine until recovery to Grade ≤ 2, and then resume with dose reduction by one level. Discontinue trastuzumab emtansine treatment if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.
ALT/AST Grade 4 ($>20.0\times$ ULN)	Discontinue trastuzumab emtansine treatment. Laboratory tests may be repeated (within 24 hours) to exclude laboratory error prior to discontinuing trastuzumab emtansine.
NRH If there are signs of portal hypertension (e.g., ascites and/or varices) and/or a cirrhosis-like pattern is seen on a CT scan of the liver, the possibility of NRH should be considered.	Discontinue trastuzumab emtansine treatment and have the patient evaluated by a hepatologist.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NRH = nodular regenerative hyperplasia; TBILI = total bilirubin; ULN = upper limit of normal.

Table 2 Trastuzumab Emtansine Dose Modification Guidelines for Hyperbilirubinemia

Severity	Action to be Taken
Grade 2 (> 1.5 to ≤ 3 × ULN)	Withhold until total bilirubin recovers to Grade ≤ 1 and then resume at the same dose level.
Grade 3 (> 3 to ≤ 10 × ULN)	Withhold until total bilirubin recovers to Grade ≤ 1 and then resume by one dose level reduction.
Grade 4 (> 10 × ULN)	Discontinue trastuzumab emtansine treatment.

ULN = upper limit of normal.

Cardiotoxicity

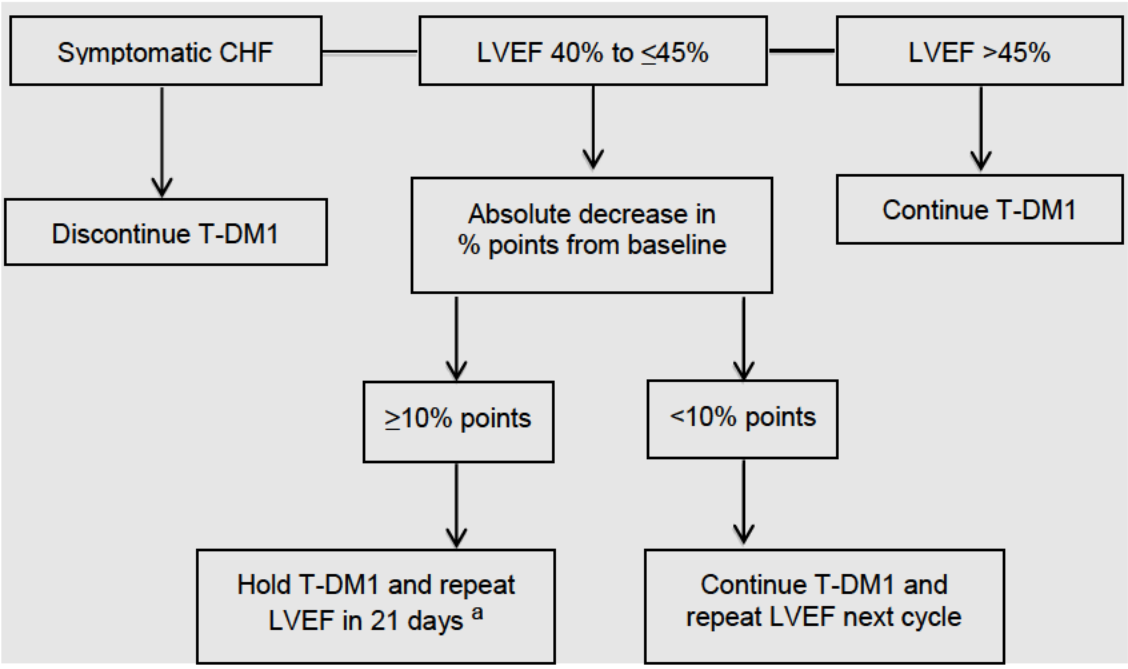
Participants without significant cardiac history and with a baseline LVEF of ≥ 55% as determined by ECHO or MUGA scan are eligible for study participation. Cardiac monitoring (ECHO/MUGA) will be performed in all participants enrolled in the Study. Assessments will occur during the screening period, pretreatment during Cycle 5 in the neoadjuvant treatment period, and pretreatment during Cycle 1, 5 (Arm C/ Arm E), 6 (Arm D), and 9 of the adjuvant treatment period, and at the treatment completion/discontinuation visit. See Section 8.2.4 and the schedule of activities (Section 1.3) for details.

Figure 1 summarizes the management of trastuzumab emtansine on the basis of LVEF measurements and changes in LVEF from baseline in participants. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement may be performed. Trastuzumab emtansine will be discontinued in any participant who develops symptomatic CHF. CHF should be treated and monitored according to standard medical practice.

The decision to stop or continue trastuzumab emtansine treatment should be on the basis of the algorithm shown in Figure 1 or asymptomatic declines in LVEF.

Trastuzumab emtansine should be discontinued in participants with symptomatic CHF and temporarily withheld in participants whose LVEF is between 45–50% and decreased ≥10% points from baseline, until clarification of LVEF change is obtained. Trastuzumab emtansine should be permanently discontinued in participants whose LVEF has been confirmed to have decreased below 45% and in participants with confirmed LVEF between 45–50% that has not recovered more than 10% points from baseline.

Figure 1 Algorithm for Continuation and Discontinuation of Trastuzumab Emtansine Treatment Based on LVEF Assessments in Participants



CHF = congestive heart failure; LVEF = left ventricular ejection fraction; T-DM1 = trastuzumab emtansine.

Note: LVEF assessment results must be reviewed before the next scheduled trastuzumab emtansine infusion.

[a] After a second consecutive confirmatory measurement is obtained, trastuzumab emtansine treatment should be discontinued if the ≥ 10% absolute LVEF decrease from baseline is confirmed.

Infusion-Related Reactions and Hypersensitivity Reactions

Prevention of anaphylactic/ hypersensitivity reactions to monoclonal antibodies is not possible: these reactions are unpredictable and can occur at any time despite preventive measures. However, participants who have had severe hypersensitivity to prior treatment with trastuzumab have a greater risk and are not recommended to receive treatment with trastuzumab emtansine.

Participants should be closely observed during the infusions, especially the first infusion, and for at least 30 minutes after infusion. The initial dose of trastuzumab emtansine should be administered as a 90-minute IV infusion.

See Table 3 for management guidelines for trastuzumab emtansine–associated infusion-related reactions and hypersensitivity reactions.

Table 3 Management Guidelines for Trastuzumab Emtansine Infusion-Related Reactions (Caused by Cytokine Release) or Hypersensitivity (Allergic) Reaction

Event	Action to Be Taken
Grade 2 reaction	Decrease trastuzumab emtansine infusion rate or interrupt infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as clinically indicated. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Pre-medication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given as clinically indicated.
Grade 3 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β–agonists, antihistamines, antipyretics, or corticosteroids, as clinically indicated. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Pre-medication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given as clinically indicated.
Grade 4 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, as clinically indicated. Monitor patient until complete resolution of symptoms. Discontinue trastuzumab emtansine.

Hematologic Toxicities

See Table 4 for trastuzumab emtansine dose modification guidelines for hematological toxicities, including thrombocytopenia.

Table 4 Trastuzumab Emtansine Dose Modification Guidelines for Hematological Toxicity

Event	Action to Be Taken
Grade ≥ 3 hematologic toxicity (other than thrombocytopenia)	*Withhold trastuzumab emtansine until recovery to Grade ≤1. Weekly CBC assessments should be performed until recovery, or as medically indicated.* *A maximum dose delay of 42 days from the last administered dose is allowed; otherwise, patients must be discontinued from trastuzumab emtansine.*
Grade 2 thrombocytopenia (50,000 to 75,0000/μL)	Assess platelet counts weekly or as medically indicated until recovery. *Hold trastuzumab emtansine* until Grade ≤ 1. Resume treatment without dose reduction. *If a patient requires two delays due to thrombocytopenia, consider reducing dose by one level.*
Grade 3 thrombocytopenia (25,000 to < 50,000/μL)	Withhold trastuzumab emtansine until recovery to Grade ≤ 1 (≥ 75,000/μL). Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 1 within 42 days after the last dose received.
Grade 4 thrombocytopenia (< 25,000/μL) at any time	*Assess platelet counts weekly or as medically indicated until recovery. H*old trastuzumab emtansine until Grade ≤ 1, *then* resume with one dose level reduction *(i.e., from 3.6 mg/kg to 3 mg/kg or from 3 mg/kg to 2.4 mg/kg). If event occurs with 2.4 mg/kg dose, discontinue trastuzumab emtansine.* Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 1 within 42 days after the last dose received.

If a participant with EBC requires two delays due to thrombocytopenia, consider reducing dose by one level.

Neuropathy

See Table 5 for trastuzumab emtansine dose modification guidelines for neuropathy.

Table 5 Trastuzumab Emtansine Dose Modification Guidelines for Neuropathy

Event	Action to Be Taken
Grade ≥ 3 peripheral neuropathy	Withhold trastuzumab emtansine until recovery to Grade ≤ 2. Following recovery, resume trastuzumab emtansine at the same dose level or with one dose level reduction, at the investigator's discretion. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.

A3–10 MANAGEMENT OF PARTICIPANTS WHO REQUIRE DOSE DELAYS AND MODIFICATIONS FOR CHEMOTHERAPY DRUGS

A3–10.1 DOSE DELAYS AND MODIFICATIONS FOR ANTHRACYCLINE-BASED CHEMOTHERAPY (DDAC AND AC)

Dose reduction and dose delays will be allowed as indicated in the relevant local prescribing information and managed as per local practice.

A3–10.2 DOSE DELAYS AND MODIFICATIONS FOR TAXANES (DOCETAXEL AND PACLITAXEL)

All dose modifications for docetaxel/paclitaxel alone are based on the dose level changes outlined below in Table 6.

Table 6 Dose Levels for Docetaxel/Paclitaxel

	Dose Level 0	Dose Level – 1	Dose Level – 2	Dose Level – 3
Paclitaxel (mg/m^2)	80 (starting dose)	64	Discontinue	—
Docetaxel (mg/m^2)	100	75 (starting dose)	60	Discontinue

Re-escalation is not permitted following a dose reduction.

A dose-limiting toxicity to docetaxel is defined as the occurrence of one or more of the following:

- Febrile neutropenia
- Grade 4 neutropenia (neutrophils $< 0.5 \times 10^9$/L) for > 5 days or a neutrophil count $< 0.1 \times 10^9$/L for more than 1 day

- Grade 2 non-hematologic adverse events (NCI CTCAE, v4), such as peripheral neuropathy, unless the toxicity is deemed manageable by the investigator (e.g., nausea and vomiting)

General dose modification guidelines:

- If a Grade 3 or 4 non-hematologic toxicity is experienced, docetaxel may be reduced from 100 mg/m^2 to 75 mg/m^2, and again to 60 mg/m^2, if required. For paclitaxel, the dose may be reduced from 80 mg/m^2 to 64 mg/m^2.
- If a taxane-related hypersensitivity reaction occurs despite pre-medication, treatment as medically indicated will be instituted.
- For hypersensitivity reaction of Grade ≤ 3, continuation of docetaxel/paclitaxel is at the investigator's discretion.
- If a Grade 4 hypersensitivity is experienced, docetaxel/paclitaxel must be permanently discontinued.
- If a Grade ≥ 3 enterocolitis is experienced, permanent discontinuation of docetaxel/paclitaxel is recommended.
- Taxane-related fluid retention will be treated as per the investigator's discretion.
- If the taxane must be discontinued before completion of the scheduled cycles, the remaining Perjeta IV and Herceptin IV or the FDC SC doses should be administered.

See Table 7 for the management of taxane-related neurosensory toxicity and

Table 8 for taxane-related musculoskeletal pain. Instructions for management of all other toxicities related to docetaxel/paclitaxel are listed in Table 9.

Table 7 Dose Modifications for Taxane-Related Neurosensory Toxicity

Paresthesias/ Dysesthesias	1–7 Days Duration	Persistent for >7 Days or Causing the Next Cycle to be Delayed
Grade 1 Paresthesias/ dysesthesias that do not interfere with function	Maintain docetaxel/ paclitaxel dose	Maintain docetaxel/ paclitaxel dose
Grade 2 Paresthesias/ dysesthesias interfering with function, but not activities of daily living	Maintain docetaxel/ paclitaxel dose [a]	Decrease docetaxel/ paclitaxel by one dose level [b]
Grade 3 Paresthesias/ dysesthesias with pain or with function impairment interfering with activities of daily living [c]	First episode: Decrease docetaxel/ paclitaxel one dose level [a] Second episode: Discontinue docetaxel/ paclitaxel	Discontinue docetaxel/ paclitaxel

[a] Must be resolved to Grade ≤1 on Day 1 of the next cycle.

[b] Hold docetaxel/paclitaxel for persistent Grade 2 neurotoxicity. When Grade ≤1, resume treatment with dose modification for docetaxel/paclitaxel. If Grade 2 toxicity persists after 3 weeks of delay, discontinue docetaxel/paclitaxel.

[c] For persistent paresthesias and dysesthesias that are disabling or life-threatening, docetaxel/paclitaxel should be discontinued.

Table 8 Dose Modifications for Taxane Musculoskeletal Pain Not Controlled by Analgesics [a]

Musculoskeletal Pain	1–7 Day Duration	Persistent for >7 Days or Causing the Next Cycle to be Delayed
Grade 1	Maintain docetaxel/ paclitaxel dose	Maintain docetaxel/ paclitaxel dose
Grade 2	Maintain docetaxel/ paclitaxel dose	Maintain docetaxel/ paclitaxel dose, OR Decrease docetaxel/ paclitaxel one dose level [b]
Grade 3	First episode: Decrease docetaxel/ paclitaxel one dose level	First episode: Decrease docetaxel/ paclitaxel one dose level [b], OR Discontinue docetaxel/ paclitaxel
	Second episode: Discontinue docetaxel/ paclitaxel	Second episode: Discontinue docetaxel/ paclitaxel

[a] The use of narcotics and non-steroidal anti-inflammatory drugs (NSAIDs) is encouraged to maintain the dose of docetaxel/paclitaxel, if possible.

[b] Delay docetaxel/paclitaxel for persistent Grade 2 or 3 musculoskeletal pain. When the symptom achieves Grade ≤1, resume treatment with dose modification for docetaxel/paclitaxel. If Grade 2 or Grade 3 toxicity persists after delay, discontinue docetaxel/paclitaxel.

Table 9 Dose Modifications and Delays for Docetaxel/Paclitaxel Alone

Adverse Event (Category) [a]	Modifications for AEs That Occur during a Cycle but Resolve prior to the Next Treatment Cycle [b]	Modifications for AEs that Require a Delay in Administration of the Treatment Cycle [c]
Hematologic: neutrophil count decreased (investigations)		
Grades 2, 3, and 4	Maintain dose.	Docetaxel: • Hold until ≥1500/mm^3. • For recovery that takes 1–3 weeks, maintain dose and add G-CSF. • If receiving G-CSF and recovery takes: – 1 week: Maintain dose. – 2–3 weeks: Decrease one dose level. Paclitaxel: • Hold until ≥1000/mm^3. • If recovery takes 1–3 weeks, maintain dose and add GCSF. • If receiving G-CSF and recovery takes: – 1 week: Maintain dose. – 2–3 weeks: Decrease one dose level.
Hematologic: platelet count decreased (investigations)		
Grades 2, 3	Maintain dose.	• Hold until ≥75,000/mm^3. • If recovery takes: – 1 week: Maintain dose. – 2–3 weeks: Decrease one dose level.
Grade 4	Decrease by one dose level.	Decrease by one dose level.

AE = adverse event; G-CSF = granulocyte colony-stimulating factor; NCI CTCAE v4 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

Notes: Dose modifications must be based on AEs that occur during the cycle (Column 2) and AEs present on the scheduled cycle Day 1 (Column 3). Dose modifications must be based on the AE requiring the greatest modification.

[a] NCI CTCAE v4.

[b] Resolved means that AEs requiring dose modification are Grade ≤1 (except absolute neutrophil/granulocyte count [which must be ≥1500/mm^3 for docetaxel and ≥1000/mm^3 for paclitaxel] and bilirubin [which must be less than or equal to the baseline grade]) on Day 1 of the next scheduled cycle (i.e., treatment can be given without delay).

[c] Hold and check weekly. With the exception of absolute neutrophil/granulocyte count and bilirubin, resume treatment when toxicity is Grade ≤1. If toxicity has not resolved after 3 weeks of delay, discontinue docetaxel and proceed with targeted therapy as planned to complete 18 cycles of treatment.

Table 9 Dose Modifications and Delays for Docetaxel/Paclitaxel Alone (cont.)

Adverse Event (Category) [a]	Modifications for AEs That Occur during a Cycle but Resolve prior to the Next Treatment Cycle [b]	Modifications for AEs That Require a Delay in Administration of the Treatment Cycle [c]
Blood and lymphatic system disorders: febrile neutropenia		
Grades 3, 4	Decrease by one dose level, add G-CSF support, or discontinue.	
Gastrointestinal disorders (if related to chemotherapy): diarrhea		
Grade 2	Maintain dose.	Decrease by one dose level.
Grade 3	Decrease by one dose level.	Decrease by one dose level.
Grade 4	Decrease by two dose levels or discontinue.	Decrease by two dose levels or discontinue.
Gastrointestinal disorders (if related to chemotherapy): mucositis oral (stomatitis)		
Grade 2	Maintain dose.	Decrease by one dose level.
Grade 3	Decrease by one dose level.	Decrease by one dose level.
Grade 4	Decrease by two dose levels or discontinue.	Decrease by two dose levels or discontinue.
Gastrointestinal disorders (if related to chemotherapy): vomiting (despite antiemetics)		
Grade 2	Decrease by one dose level (optional).	Decrease by one dose level.
Grades 3, 4	Decrease by one dose level or discontinue.	Decrease by two dose levels or discontinue.

AE = adverse event; G-CSF = granulocyte colony-stimulating factor; NCI CTCAE v4 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

Notes: Dose modifications must be based on AEs that occur during the cycle (Column 2) and AEs present on the scheduled cycle Day 1 (Column 3). Dose modifications must be based on the AE requiring the greatest modification.

[a] NCI CTCAE v4.

[b] Resolved means that AEs requiring dose modification are Grade ≤ 1 (except absolute neutrophil/granulocyte count [which must be $\geq 1500/mm^3$ for docetaxel and $\geq 1000/mm^3$ for paclitaxel] and bilirubin [which must be less than or equal to the baseline grade]) on Day 1 of the next scheduled cycle (i.e., treatment can be given without delay).

[c] Hold and check weekly. With the exception of absolute neutrophil/granulocyte count and bilirubin, resume treatment when toxicity is Grade ≤ 1. If toxicity has not resolved after 3 weeks of delay, discontinue docetaxel and proceed with targeted therapy as planned to complete 18 cycles of treatment.

Table 9 Dose Modifications and Delays for Docetaxel/Paclitaxel Alone (cont.)

Adverse Event (Category) [a]	Modifications for AEs That Occur during a Cycle but Resolve prior to the Next Treatment Cycle [b]	Modifications for AEs That Require a Delay in Administration of the Treatment Cycle [c]
Gastrointestinal disorders (if related to chemotherapy): enterocolitis [d]		
Grades 3, 4	Provide immediate supportive care and discontinue (at the discretion of the investigator)	
Hepatic function: bilirubin or AST or ALP increased (investigations)		
Grade 2	Decrease by one dose level.	• Hold until bilirubin returns to the baseline grade, and AST and ALP have returned to Grade ≤1. • Subsequently decrease by one dose level.
Grade 3	Decrease by two dose levels.	Decrease by two dose levels.
Grade 4	Discontinue.	Discontinue.
Other clinically significant AEs [e]		
Grade 3	Decrease by one dose level.	Decrease by one dose level.
Grade 4	Decrease by two dose levels or discontinue.	Discontinue.

AE = adverse event; G-CSF = granulocyte colony-stimulating factor; NCI CTCAE v4 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

Notes: Dose modifications must be based on AEs that occur during the cycle (Column 2) and AEs present on the scheduled cycle Day 1 (Column 3). Dose modifications must be based on the AE requiring the greatest modification.

[a] NCI CTCAE v4.

[b] Resolved means that AEs requiring dose modification are Grade ≤1 (except absolute neutrophil/granulocyte count [which must be ≥1500/mm^3 for docetaxel and ≥1000/mm^3 for paclitaxel] and bilirubin [which must be less than or equal to the baseline grade]) on Day 1 of the next scheduled cycle (i.e., treatment can be given without delay).

[c] Hold and check weekly. With the exception of absolute neutrophil/granulocyte count and bilirubin, resume treatment when toxicity is Grade ≤1. If toxicity has not resolved after 3 weeks of delay, discontinue docetaxel and proceed with targeted therapy as planned to complete 18 cycles of treatment.

[d] Recognition of symptoms of severe enterocolitis is critical as this requires appropriate supportive care. In case of symptoms of abdominal pain with tenderness, fever, diarrhea and mucositis, with or without neutropenic fever, supportive care should be started immediately.

[e] Determination of clinically significant AEs is at the discretion of the investigator.

Appendix 4
Collection of Pregnancy Information

TABLE OF CONTENTS

A4–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within seven months after the final dose of study drug. 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 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 *Sharing* 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 seven months after the final dose of study drug. 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 the Use and *Sharing* 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 *Sharing* 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 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 (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
Patient Preference Questionnaire for the Adjuvant Phase

PATIENT PREFERENCE QUESTIONNAIRE

During the second phase of treatment, given after surgery, pertuzumab + trastuzumab (fixed dose combination) can be administered in 2 settings:

1. through a needle injected into your thigh, called a subcutaneous or SC injection **at home**
2. through a needle injected into your thigh, called a subcutaneous or SC injection **in the hospital**

We are interested in understanding your experiences and your preferences for this phase of your treatment.

Please answer the following question about your experience. There are no right or wrong answers.

1) All things considered, which setting for your treatment did you prefer?

□ Hospital □ Home □ No preference

2) If you have a preference for one of the settings for your treatment, how strong is this preference?

□ Very strong □ Fairly strong □ Not very strong

3) If you have a preference for one of the settings for your treatment, what are the **TWO** main reasons for your preference?

□ Less stressful

□ Time and cost saving

□ Feels safe

□ Feels more comfortable

□ Reduces my risk of infection, such as COVID-19

□ I can continue with my cancer treatment

□ Other reason; please specify: ……..……

Please use the space below for any other comments you would like to add:

Appendix 6
Healthcare Professional Questionnaire: Neoadjuvant Phase – Drug Preparation Area

Healthcare Professional Experiences and Preferences for either Pertuzumab and Trastuzumab Fixed-Dose Combination Subcutaneous Injection (PH FDC SC / Phesgo®) or Pertuzumab® and Trastuzumab® Intravenous Infusion (P+H IV) for the Treatment of Patients with Early or Locally Advanced/Inflammatory HER2-positive Breast Cancer.

Healthcare Professional Survey

This Qualitative Survey is to be completed by healthcare professionals (HCPs) who have had experience in preparing and/or administering both pertuzumab and trastuzumab fixed-dose combination (FDC) for subcutaneous (SC) injection (Phesgo), and/*or* pertuzumab intravenous and trastuzumab intravenous (P+H IV) infusions, as part of the MO43110 clinical study.

An HCP is defined as any personnel involved in the drug preparation and/or drug administration processes. Patient chair time (see Table 1) includes P+H IV and PH FDC SC administration time and should be based on “time of day” measurements (min/h). Active HCP time will be measured for chronologically listed, pre-selected tasks (Table 2) for P+H IV and PH FDC SC preparation / administration, both in the drug preparation area (DPA, drug preparation time) and treatment area (drug administration time). Active HCP time should be based on “stopwatch time” measurements (min/sec).

Table 1 Study definitions

Term	Definition
Patient chair time	Time between entry and exit of the infusion chair
Treatment administration duration	Time between initiation and completion of the treatment administration
Active HCP time	Time spent by staff member carrying out pre-specified tasks dedicated to a patient
Treatment area	The place where P+H IV or PH FDC SC treatments are administered
Drug preparation area	The place where P+H IV and PH FDC SC are prepared before they are administered. This may refer to the hospital pharmacy or day oncology unit

Appendix 6: HCPQ for Neoadjuvant Phase – Drug Preparation Area

Table 2 Chronological listing of tasks

Task	P+H IV	PH FDC SC
Drug preparation area		
Collection of pertuzumab and trastuzumab (includes IV consumables and time to reach aseptic preparation area; SC vial checks), reconstitution of IV pertuzumab and trastuzumab, SC filling, sign-off of prepared IV pertuzumab and trastuzumab bags/dispensed SC formulation	X	X
Treatment area		
Installation of venous catheter/line flushing	X	
Pre-medication administration (if indicated)	X	X
Bringing IV bag to patient chair	X	
PH FDC SC vial check and filling (if not done in drug preparation area)		X
P+H IV infusion initiations	X	
PH FDC SC administration and immediate monitoring		X
Patient monitoring during infusion	X	
Disconnecting infusion/flushing line/disposing of materials	X	
Disposing of PH FDC SC vials and syringes		X
Patient monitoring post-infusion/post-injection (only “active” monitoring time in the treatment area to be collected)	X	X

IV, intravenous; SC, subcutaneous.

This survey will take approximately 5 minutes to complete.

You are being invited to complete this survey because your centre is a MO43110 clinical study site.

Appendix 6: HCPQ for Neoadjuvant Phase – Drug Preparation Area

Questions 1a – 1b should be completed for every patient after each treatment cycle $with$ P+H IV or PH FDC SC, during the neoadjuvant phase of the study.

Questions 2 – 4 should be completed for each patient after the last treatment cycle at the conclusion of the neoadjuvant phase.

The objective of this survey is to obtain feedback from key HCPs within the pharmacy/drug preparation area where Perjeta®, Herceptin® and Phesgo® are prepared and dispensed. We are interested in the following:

1. HCP's perceived differences in the management of Perjeta-Herceptin® treatments at the healthcare centre, comparing PH FDC SC injection with P+H IV infusion

2. HCP's treatment preferences and perceptions of the time required to complete tasks associated with PH FDC SC injection compared with P+H IV infusion

Your confidentiality will be respected, and none of the information we receive will be used in a way that could identify you.

Study ID: _____

Site ID: _____

Patient ID: _____

Cycle Number: _____

Date of treatment: _____ (dd/mm/yyyy)

Healthcare Professional Respondent (please indicate):

☐ Pharmacist / Pharmacy Technician

☐ Nurse

Other (specify): _____

DATE OF COMPLETION: ___/___ / ____ (dd/mm/yyyy)

Experience with PH FDC SC and P+H IV infusion dispensing and preparation

Please complete Questions 1a and 1b for each patient treatment cycle.

1a. Please indicate which treatment preparation the estimates relate to:

☐ PH FDC SC ☐ P+H IV

1b. How long did it take to prepare the treatment for use?

…….. (Please estimate to the nearest minute)

Please indicate any factors during the preparation that may have affected the timing estimate (if any):

……
……
……
……
……

2. ***In your opinion, i*****f all P+H IV infusions were switched to PH FDC SC injections, please indicate how strongly you agree or disagree with each of the following statements[1].**

	One "X" only					
	Strongly Disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**	**Not applicable**
a. Staff will have increased availability for other tasks in the pharmacy (e.g. reconstituting other drugs, performing more frequent or timely inventory checks, more timely responses to queries from other departments, etc.)						
b. Administrative procedures *related to* PH FDC SC require less time (i.e., worksheet, release form, labels, etc.)						
c. Using PH FDC SC provides more flexibility for pharmacy staff in managing their workload						
d. As PH FDC SC is fixed-dose, potential dosing errors are avoided						
e. As PH FDC SC is fixed-dose, there is less drug wastage (i.e. un-used / leftover drug in IV vial)						
f. Less storage space for PH FDC SC-related supplies is required in the pharmacy, as there is no need for reconstitution						
g. Number of preparation steps and staff time commitment are reduced						
Please use this box for any additional comments:						

1 Statements are hypotheses and not actual claims

Questions 3 and 4 are only applicable for patients who switched from Arm A to Arm B. If the patient did not switch, please select 'not applicable'.

Considering the drug preparation of Perjeta (IV), Herceptin (IV) and PH FDC SC (Phesgo SC):

3. Which took less time *(excluding observation period)*?

☐ P+H IV ☐ PH FDC SC ☐ no difference ☐ *not applicable*

4. Which required less use of institutional resources (e.g. staff time, facility costs, equipment use)?

☐ P+H IV ☐ PH FDC SC ☐ no difference ☐ *not applicable*

Appendix 7
Healthcare Professional Questionnaire: Neoadjuvant Phase – Administering Treatment

Healthcare Professional Experiences and Preferences for either Pertuzumab and Trastuzumab Fixed-Dose Combination Subcutaneous Injection (PH FDC SC / Phesgo®) or Pertuzumab® and Trastuzumab® Intravenous Infusion (P+H IV) for the Treatment of Patients with Early or Locally Advanced/Inflammatory HER2-positive Breast Cancer.

Healthcare Professional Survey

This Qualitative Survey is to be completed by healthcare professionals (HCPs) who have had experience in preparing and/or administering both pertuzumab and trastuzumab fixed-dose combination (FDC) for subcutaneous (SC) injection (Phesgo), and pertuzumab intravenous and trastuzumab intravenous (P+H IV) infusions, as part of the MO43110 clinical study.

An HCP is defined as any personnel involved in the drug preparation and/or drug administration processes. Patient chair time (see Table 1) includes P+H IV and PH FDC SC administration time and should be based on “time of day” measurements (min/h). Active HCP time will be measured for chronologically listed, pre-selected tasks (Table 2) for P+H IV and PH FDC SC preparation / administration, both in the drug preparation area (DPA, drug preparation time) and treatment area (drug administration time). Active HCP time should be based on “stopwatch time” measurements (min/sec).

Table 1 Study definitions

Term	Definition
Patient chair time	Time between entry and exit of the infusion chair
Treatment administration duration	Time between initiation and completion of the treatment administration
Active HCP time	Time spent by staff member carrying out pre-specified tasks dedicated to a patient
Treatment area	The place where P+H IV or PH FDC SC treatments are administered
Drug preparation area	The place where P+H IV and PH FDC SC are prepared before they are administered. This may refer to the hospital pharmacy or day oncology unit

Table 2 Chronological listing of observed tasks

Task	P+H IV	PH FDC SC
Drug preparation area		
Collection of pertuzumab and trastuzumab (includes IV consumables and time to reach aseptic preparation area; SC vial checks), reconstitution of IV pertuzumab and trastuzumab, SC filling, sign-off of prepared IV pertuzumab and trastuzumab bags/dispensed SC formulation	X	X
Treatment area		
Installation of venous catheter/line flushing	X	
Pre-medication administration (if indicated)	X	X
Bringing IV bag to patient chair	X	
PH FDC SC vial check and filling (if not done in drug preparation area)		X
P+H IV infusion initiations	X	
PH FDC SC administration and immediate monitoring		X
Patient monitoring during infusion	X	
Disconnecting infusion/flushing line/disposing of materials	X	
Disposing of PH FDC SC vials and syringes		X
Patient monitoring post-infusion/post-injection (only “active” monitoring time in the treatment area to be collected)	X	X

IV, intravenous; SC, subcutaneous.

This survey will take approximately 5 minutes to complete.

You are being invited to complete this survey because your centre is a MO43110 clinical study site.

Appendix 7: HCPQ for Neoadjuvant Phase – Administering Treatment

Questions 1a – 1g should be completed for every patient after each treatment cycle $with$ P+H IV or PH FDC SC during the neoadjuvant phase of the study.

Questions 2 – 11 should be completed for each patient after the last treatment cycle at the conclusion of the neoadjuvant phase.

The objective of this survey is to obtain feedback from key HCPs in the treatment area where Perjeta®, Herceptin® and Phesgo® are administered. We are interested in the following:

1. HCP's perceived differences in the management of Perjeta-Herceptin® treatments at the healthcare centre, comparing PH FDC SC injection with P+H IV infusion

2. HCP's treatment preferences and perceptions of the time required to complete tasks associated with PH FDC SC injection compared with P+H IV infusion

Your confidentiality will be respected, and none of the information we receive will be used in a way that could identify you.

Study ID: _____

Site ID: _____

Patient ID: _____

Cycle Number: _____

Date of treatment: _____ (dd/mm/yyyy)

Healthcare Professional Respondent (please indicate):

☐ Nurse

☐ Treating Doctor

Other (specify): _____

DATE OF COMPLETION: / / (dd/mm/yyyy)

Experience with PH FDC SC injection and P+H IV infusion administration

Please complete Questions 1a – 1g for each patient treatment cycle.

1a. Please indicate which treatment the estimates relate to:

☐ PH FDC SC (proceed to *Q1f*) ☐ P+H IV (proceed to Q1b)

1b. Did the patient have existing IV access?

☐ YES (proceed to Q1d) ☐ NO (proceed to Q1c)

1c. If new IV access was needed for this cycle of treatment, please indicate what type of IV access was provided and how long (in minutes) this took to set up?

☐ peripheral vein cannulation

☐ PICC, peripherally inserted central catheter

☐ Port-a-Cath

☐ tunneled central venous catheter

…….. (Please estimate to the nearest minute)

1d. What type of existing IV access did the patient have? Assumes indwelling IV access

☐ PICC, peripherally inserted central catheter

☐ Port-a-Cath

☐ tunneled central venous catheter

1e. When did the existing IV access place? Assumes indwelling IV access

☐ within 7 days prior today ☐ > 7 < 14 days prior today

☐ > 14 < 30 days prior today ☐ Other. Please specify: ……

1f. How long (in minutes) did it take to administer the treatment (P+H IV or PH FDC SC)?

…….. (Please estimate to the nearest minute)

1g. How long (in minutes) was the patient in the Treatment Area in total?

…….. (Please estimate to the nearest minute)

Please indicate any factors during the treatment in the Treatment Area that may have affected the timing estimate (if any):

……
……
……

Impact on Clinical Management and Clinical Efficiency

2. ***In your opinion, i*****f all P+H IV infusions were switched to PH FDC SC injections, please indicate how strongly you agree or disagree with each of the following statements[1]. When answering question 2, please only consider P+H IV and PH FDC SC and not other IV treatment options.**

	One "X" only					
	Strongly Disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**	**Not applicable**
a. Patients may be moved out of the Treatment Area (for infusion treatment) to receive PH FDC SC injections (e.g., outpatient procedure room)						
b. PH FDC SC's SC route of administration allows for more flexible treatment scheduling (i.e., patient visits are not confined to availability of infusion chairs)						
c. Frees up infusion chairs for patients whose treatments can only be given IV						
d. Waiting list for any P+H IV treatment at the Treatment Area is reduced						
e. Staff's work burden is reduced, enhancing work performance						
f. More interaction time between HCPs and patients (e.g., for patient education)						
g. Staff have more time for further professional education/development.						
h. Staff has more time for administrative tasks (e.g., efficient chart completion, appointment scheduling, returning patient phone calls, etc.)						
i. Patients on PH FDC SC spend less time in the Treatment Area						
j. Patients prefer PH FDC SC to P+H IV						
Please use this box to add any additional comments:						

1 Statements are hypotheses and not actual claims

[Please consider the standard practice at your site, even if the process deviates somewhat from what is described below.]

Questions 3–11 are only applicable for patients who switched from Arm A to Arm B. If the patient did not switch, please select 'not applicable'.

Considering the administration of Perjeta (IV), Herceptin (IV) versus PH FDC SC (Phesgo SC):

3. Which was more convenient for the patient?

☐ P+H IV ☐ PH FDC SC ☐ no difference ☐ unsure ☐ *not applicable*

4. Which was better for optimising patient care at your institution?

☐ P+H IV ☐ PH FDC SC ☐ no difference ☐ unsure ☐ *not applicable*

5. Which required less time to administer (excluding observation period)?

☐ P+H IV ☐ PH FDC SC ☐ no difference ☐ *not applicable*

6. Which required less use of institutional resources (e.g., staff time, facility costs, equipment use)?

☐ P+H IV ☐ PH FDC SC ☐ no difference ☐ *not applicable*

7. Which required less time to administer all the treatment (including IV chemotherapy):

☐ P+H IV ☐ PH FDC SC ☐ no difference ☐ *not applicable*

8. Which allowed for attending to more patients because of time savings from the mode of administration of pertuzumab and trastuzumab?

☐ P+H IV ☐ PH FDC SC ☐ no difference ☐ *not applicable*

9. During this neoadjuvant phase you had to administer IV chemotherapy through patient´s IV access. You prefer to accompany IV chemotherapy with:

☐ P+H IV ☐ PH FDC SC ☐ no difference ☐ *not applicable*

10. Which was preferred by patients?

☐ P+H IV ☐ PH FDC SC ☐ no difference ☐ unsure ☐ *not applicable*

Please provide a reason for your choice of response to Q10:

.....
.....
.....
.....

11. How frequently would you recommend PH FDC SC administration to your patients in the future?

☐ always ☐ sometimes ☐ never ☐ *not applicable*

Appendix 8
Health-related Quality of Life Questionnaire

European Organization European Organization for Research and Treatment of Cancer
Quality of Life Questionnaire C30

ENGLISH

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

ENGLISH

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

Appendix 9
Healthcare Professional Questionnaire: Adjuvant Phase – Drug Preparation Area

Healthcare Professional Experience and Preference for Pertuzumab and Trastuzumab Fixed-Dose Combination Subcutaneous Injection (PH FDC SC; Phesgo®) administered at Home or in Hospital, for the Treatment of Patients with Early or Locally Advanced/Inflammatory HER2-positive Breast Cancer.

Healthcare Professional Survey

This Qualitative Survey is to be completed by healthcare professionals (HCPs) who have had experience in preparing and/or administering pertuzumab and trastuzumab fixed-dose combination (FDC) for subcutaneous (SC) injection (Phesgo) in hospital or in the patient's home, as part of the MO43110 Clinical Study.

An HCP is defined as any personnel involved in the drug preparation and/or drug administration processes. Patient treatment time (see Table 1) includes PH FDC SC administration time and should be based on "time of day" measurements (min/h). Active HCP time will be measured for chronologically listed, pre-selected tasks (Table 2) for PH FDC SC processes. Active HCP time should be based on "stopwatch time" measurements (min/sec).

Table 1 Study definitions

Term	Definition
Patient treatment time	Time between entry and exit of the patient's home or hospital treatment area
SC administration duration	Time between initiation and completion of SC injection
Active HCP time	Time spent by staff member carrying out pre-specified tasks dedicated to a patient
Treatment area	The place where PH FDC SC is administered
Drug preparation area	The place where PH FDC SC is prepared before it is administered. This may refer to the patient's home, hospital pharmacy or day oncology unit

Table 2 Chronological listing of tasks

Task	PH FDC SC
Drug preparation area	
Collection of PH FDC SC (includes time to reach aseptic preparation area where applicable; and SC vial checks), SC filling, sign-off of dispensed SC formulation	X
Treatment area	
Pre-medication administration (if indicated)	X
PH FDC SC vial check and filling (if not done in drug preparation area)	X
PH FDC SC administration and immediate monitoring	X
Disposing of PH FDC SC vials and syringes	X
Patient monitoring post-injection (only “active” monitoring time in the treatment area to be collected)	X

SC, subcutaneous.

This survey will take approximately 5 minutes to complete.

You are being invited to complete this survey because your centre is a MO43110 clinical study site.

Questions 1a – 1c should be completed for every patient after treatment with PH FDC SC twice during the cross over period: once after the last cycle of PH FDC SC administered in the home setting during the cross-over period and once after the last cycle of PH FDC SC administered in the hospital setting during the cross-over period.

Questions 2 – 4 should be completed for each patient after administration of the last cycle of study treatment in the cross-over period.

Appendix 9: HCPQ for Adjuvant Phase – Drug Preparation Area

The objective of this survey is to obtain feedback from key HCPs regarding the time spent and resources required for PH FDC SC preparation in hospital or at the patient´s home.

Your confidentiality will be respected, and none of the information we receive will be used in a way that could identify you.

Study ID: _____

Site ID: _____

Patient ID: _____

Cycle Number: _____

Date of treatment: _____ (dd/mm/yyyy)

Healthcare Professional Respondent (please indicate):

☐ Nurse

☐ Pharmacist / Pharmacy Technician

Other (specify): _____

DATE OF COMPLETION: ___/___ / ____ (dd/mm/yyyy)

PH FDC SC administration setting:

☐ Hospital

☐ Patient´s home

Appendix 9: HCPQ for Adjuvant Phase – Drug Preparation Area

1a. Where was the treatment prepared?

☐ Patient´s home ☐ Hospital pharmacy ☐ Day oncology unit

☐ Other. Please specify: ……

If the preparation was in a place other than patient´s home, please specify the reason:

……

1b. How long did it take to prepare the treatment for use?

If the preparation was in a place other than the patient's home, please also include the time from the preparation place to reach the patient's home.

Time for treatment preparation: …….. (Please estimate to the nearest minute)

Time from the preparation place to reach the patient's home: ……...
(Please estimate to the nearest minute only if applies)

1c. Which healthcare professionals were involved in the treatment preparation processes?

☐ Physician ☐ Nurse ☐ Pharmacist ☐ All of them

☐ Others: ……

Please indicate any factors during the preparation that may have affected the timing estimate (if any):

……
……
……
……

2. If all PH FDC SC injections were switched from an in-hospital setting to the patient´s home, please indicate how strongly you agree or disagree with each of the following statements[1].

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree	Not applicable
a. Staff will have increased availability for other tasks in the hospital´s pharmacy (e.g., reconstituting other drugs, performing more frequent or timely inventory checks, more timely responses to queries from other departments, etc.)						
b. Administrative procedures related to PH FDC SC will require less time (i.e., worksheet, release form, labels, etc.)						
c. Number of preparation steps and staff time commitment are reduced						
Please use this box to add any additional comments:						

[1]Statements are hypotheses and not actual claims

Considering the drug preparation of PH FDC SC:

3. Which took less time?

☐ Patient´s home ☐ In Hospital ☐ no difference ☐ unsure

4. Which required less use of institutional resources (e.g., staff time, facility costs, equipment use)?

☐ Patient´s home ☐ In Hospital ☐ no difference ☐ unsure

Appendix 10
Healthcare Professional Questionnaire: Adjuvant Phase – Administering Treatment

Healthcare Professional Experience and Preference for Pertuzumab and Trastuzumab Fixed-Dose Combination Subcutaneous Injection (PH FDC SC; Phesgo®) administered at Home or in Hospital, for the Treatment of Patients with Early or Locally Advanced/Inflammatory HER2-positive Breast Cancer.

Healthcare Professional Survey

This Qualitative Survey is to be completed by healthcare professionals (HCPs) who have had experience in preparing and/or administering pertuzumab and trastuzumab fixed-dose combination (FDC) for subcutaneous (SC) injection (Phesgo) in hospital or in the patient's home, as part of the MO43110 Clinical Study.

An HCP is defined as any personnel involved in the drug preparation and/or drug administration processes. Patient treatment time (see Table 1) includes PH FDC SC administration time and should be based on "time of day" measurements (min/h). Active HCP time will be measured for chronologically listed, pre-selected tasks (Table 2) for PH FDC SC processes. Active HCP time should be based on "stopwatch time" measurements (min/sec).

Table 1 Study definitions

Term	Definition
Patient treatment time	Time between entry and exit of the patient's home or hospital treatment area
SC administration duration	Time between initiation and completion of SC injection
Active HCP time	Time spent by staff member carrying out pre-specified tasks dedicated to a patient
Treatment area	The place where PH FDC SC is administered
Drug preparation area	The place where PH FDC SC is prepared before it is administered. This may refer to the patient's home, hospital pharmacy or day oncology unit

Table 2 Chronological listing of observed tasks

Task	PH FDC SC
Drug preparation area	
Collection of PH FDC SC (includes time to reach aseptic preparation area where applicable; SC vial checks), SC filling, sign-off of dispensed SC formulation	X
Treatment area	
Pre-medication administration (if indicated)	X
PH FDC SC vial check and filling (if not done in drug preparation area)	X
PH FDC SC administration and immediate monitoring	X
Disposing of PH FDC SC vials and syringes	X
Patient monitoring post-injection (only “active” monitoring time in the treatment area to be collected)	X

SC, subcutaneous.

This survey will take approximately 5 minutes to complete.

You are being invited to complete this survey because your centre is a MO43110 clinical study site.

Questions 1a – 1i should be completed for every patient after the treatment with PH FDC SC twice during the cross over period: once after the last cycle of PH FDC SC administered in the home setting during the cross-over period and once after the last cycle of PH FDC SC administered in the hospital setting during the cross-over period.

Questions 1j – 1l and 2 – 7 should be completed for each patient after administration of the last cycle of study treatment in the cross-over period.

Appendix 10: HCPQ for Adjuvant Phase – Administering Treatment

The objective of this survey is to obtain feedback from key HCPs regarding the time spent and resources required for PH FDC SC administration in hospital or at the patient´s home.

Your confidentiality will be respected, and none of the information we receive will be used in a way that could identify you.

Study ID: _____

Site ID: _____

Patient ID: _____

Cycle Number: _____

Date of treatment: _____ (dd/mm/yyyy)

Healthcare Professional Respondent (please indicate):

☐ Nurse

☐ Treating Doctor

Other (specify): _____

DATE OF COMPLETION: ___/___ / ____ (dd/mm/yyyy)

PH FDC SC administration setting:

☐ Hospital

☐ Patient´s home

Appendix 10: HCPQ for Adjuvant Phase – Administering Treatment

1a. How long did it take to travel to the patient´s home to administer PH FDC SC?

…….. (Please estimate to the nearest minute) ☐ N/A

1b. How long did it take for the patient to travel to the hospital to receive PH FDC SC? *Ask the patient.*

…….. (Please estimate to the nearest minute) ☐ N/A

1c. How long (in minutes) did it take to administer PH FDC SC, i.e., SC administration duration?

…….. (Please estimate to the nearest minute)

1d. How long (in minutes) was the patient treatment time? (see Table 1 for definition, includes monitoring time)

…….. (Please estimate to the nearest minute)

1e. If receiving PH FDC SC in hospital, how much time (in minutes) did the patient spend in hospital? From arrival to departure time. *Ask patient her hospital arrival time.*

…….. (Please estimate to the nearest minute) ☐ N/A

1f. If receiving PH FDC SC at home, how much time (in minutes) did you spend at the patient's home? From arrival to departure time

…….. (Please estimate to the nearest minute) ☐ N/A

Please indicate any factors during the treatment in the Treatment Area that may have affected the timing estimate (if any):

……
……
……

1g. Does the patient still have implanted (e.g., Port-a-Cath, PICC line) IV access?

☐ Yes ☐ No

1h. If your answer in the question 1g. was "No", when was the IV access removed?

☐ After surgery and before initiating adjuvant treatment

☐ After initiating adjuvant treatment

☐ N/A

Based on your answer, please specify the date: ……

1i. If your answer in the question 1g. was "Yes":

What is the main reason to keep the IV access? Mark all that apply

☐ Local protocol ☐ Risk of recurrence ☐ Patient preference ▱ N/A

☐ Other. Please specify: ……

1j. How long do you keep implanted IV access in early HER2-positive Breast Cancer patients with pCR following surgery in your institution?

☐ < 12 months ☐ ≥ 12 months ☐ 18 months ☐ < 24 months ☐ ≥ 24 months

1k. When is the decision point for you to decide to remove IV access for early HER2-positive Breast Cancer patients?

☐ Before surgery

☐ After surgery

☐ After pCR results

☐ After completion of full adjuvant therapy

☐ After completion of IV antineoplastic within adjuvant therapy

☐ Other. Please specify: ……

1l. Do you consider it necessary to keep implanted IV access knowing that the patient's treatment will be SC until the full 18 cycles?

☐ Yes ☐ No ☐ Unsure

2. If all PH FDC SC injections were switched from an in-hospital setting to the patient´s home, please indicate how strongly you agree or disagree with each of the following statements[1].

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree	Not applicable
a. PH FDC SC's SC route of administration allows for more flexible treatment scheduling (i.e., patient visits are not confined to availability of infusion chairs)						
b. Frees up infusion chairs or outpatient procedure rooms used to administer SC injections						
c. Waiting list for infusion chairs or outpatient procedure rooms is reduced						
d. Staff's work burden is reduced, enhancing work performance						
e. More interaction time between HCPs and patients on IV treatment (e.g., for patient education)						
f. Staff has more time for administrative tasks (e.g., efficient chart completion, appointment scheduling, returning patient phone calls, etc.)						
g. Patients will spend less time in hospital						
h. Patients prefer PH FDC SC at home						
Please use this box to add any additional comments:						

[1]Statements are hypotheses and not actual claims

Considering the administration of PH FDC SC:

3. Which was more convenient for the patient?

☐ Patient´s home ☐ In Hospital ☐ no difference ☐ unsure

4. Which was better for optimising patient care?

☐ Patient´s home ☐ In Hospital ☐ no difference ☐ unsure

5. Which required less use of institutional resources (e.g., staff time, facility costs, equipment use)?

☐ Patient´s home ☐ In Hospital ☐ no difference ☐ unsure

6. Which was preferred by patients?

☐ Patient´s home ☐ In Hospital ☐ no difference ☐ unsure

7. How frequently would you recommend PH FDC SC at home to your patients in the future?

☐ always ☐ sometimes ☐ never

Please provide a reason for your choice of response to Q7:

.....
.....
.....
.....

Appendix 11
Clinical Safety Laboratory Tests

All female participants of childbearing potential (refer to Section 5.1.1 for definition) will have a serum pregnancy test performed at screening within 7 days prior to the first administration of study medication (with result available prior to dosing). Urine pregnancy tests should be repeated during the treatment period within 7 days prior to Cycle 3 and at last cycle of neoadjuvant phase (and as clinically indicated), at Cycle 1, 5 or 6, 9, and last cycle during adjuvant phase, as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. Pregnancy test at 7 months (i.e., between 6–9 months follow up) can be performed if indicated.

The tests detailed in Table 1 below will be performed by the local laboratory.

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.

Table 1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). • Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. Albumin should be measured at Screening for determining participant eligibility. Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN. • HIV serology: HIV-1 antibody/ HIV-2 antibody • HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test • HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test • Pregnancy test

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LDH = lactate dehydrogenase; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell.

Investigators must document their review of each laboratory safety report.

Appendix 12
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
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 selfcare but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited selfcare, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 13
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine or equivalent for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.

   During home administration of study treatment, blood pressure and respiratory rate should be measured approximately every 5 minutes. Pulse rate and oxygen saturation will be continuously monitored using the pulse oximeter. Vital signs will be measured until symptoms have fully resolved or emergency medical services arrive.
5. Administer antihistamines, epinephrine or equivalent, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.

Appendix 14
NYHA Functional Classification System for Heart Failure and LVSD NCI CTCAE V5.0 Grading

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.

LVSD NCI CTCAE V5 Grading

Investigations					
	Grade				
	1	**2**	**3**	**4**	**5**
EF 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) or cardiac imaging abnormalities	Symptoms with moderate 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 so only at an elevation in the filling pressure.

https://www.eortc.be/services/doc/ctc/CTCAE_v5_Quick_Reference_5x7.pdf

Appendix 15
Home Administration Instructions for Mobile Healthcare Professional

Pertuzumab and trastuzumab fixed-dosed combination formulation for subcutaneous administration (PH FDC SC) should be administered by a healthcare professional. Self-administration is not allowed.

The Mobile Clinical Services Training Manual contains additional detail on the administration of PH FDC SC in the home setting. The mobile healthcare professional should follow the instructions in the Mobile Clinical Services Training Manual.

Materials needed for Subcutaneous Injection in the Home Setting

- PH FDC SC vials
- Syringe
- Transfer needle (18 – 21G hypodermic needle)
- 25G-27G (3/8”-5/8”) hypodermic injection needle
- Sharps disposal container
- Alcohol wipes

Preparation for Administration

- PH FDC SC vials should be stored at 2ºC to 8ºC (36ºF to 46ºF) in the original carton until time of use. Keep PH FDC SC out of the reach of children and pets.
- Before use, allow the PH FDC SC vial to warm up to room temperature for about 15 minutes before preparing an injection.
- PH FDC SC should be inspected for particulate matter and discoloration before administration. Do not use vial if particulates or discoloration is present. Do not shake.
- Both dose strengths are ready to use for subcutaneous injection and should not be diluted.
- A syringe, a transfer needle and an injection needle are needed to withdraw PH FDC SC solution from the vial and inject it subcutaneously. PH FDC SC may be injected using 25G-27G (3/8”-5/8”) hypodermic injection needles.
- To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration followed by volume adjustment to 15 mL (loading dose) and 10 mL (maintenance dose).
- PH FDC SC is compatible with stainless steel, polypropylene, polycarbonate, polyethylene, polyurethane, polyvinyl chloride, and fluorinated ethylene polypropylene.
- If the dose is not to be administered immediately, prepare the dosing syringe in controlled and validated aseptic conditions.

- After the solution of PH FDC SC is withdrawn from the vial and into the syringe, replace the transfer needle with a syringe closing cap.
- Administer PH FDC SC within 24 hours. If the syringe containing PH FDC SC is not used immediately, the syringe can be stored in the refrigerator (2°C to 8°C) and at room temperature (20°C to 25°C, 68°F to 77°F) for up to 4 hours.
- PH FDC SC is for single use only. Discard any unused portion remaining in the vial.
- Dispose of transfer needles, injection needles, caps, and used syringes in a sharps disposal container. Keep the sharps disposal container out of reach of children and pets.

Administration

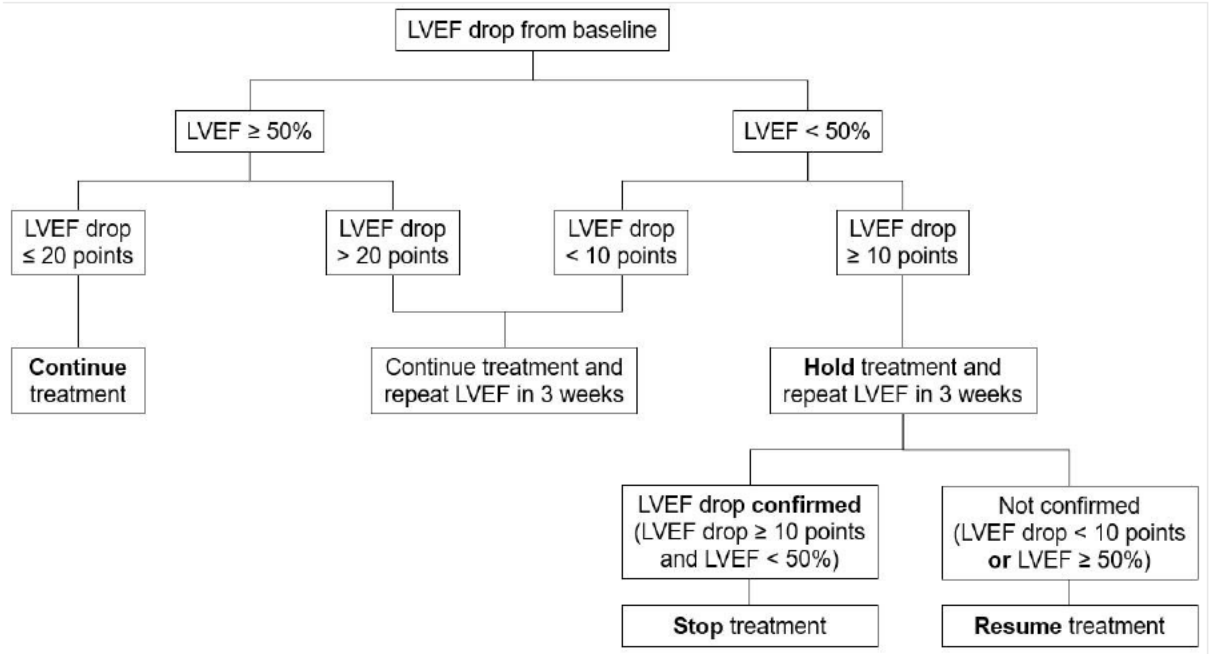
The thigh is the only location where PH FDC SC should be administered. The subcutaneous injection site should be alternated between the left and right thigh. New injections should be given at a distance of at least 1 inch/2.5 cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. Do not split the dose between two syringes or between two sites of administration. During the treatment course with PH FDC SC, other medications for subcutaneous administration should preferably be injected at different sites.

All doses of the PH FDC SC will be administered over 5–8 minutes as a SC injection into the thigh at a rate of no more than 2 mL/min. Participants who have had ≥ 6 weeks since their last P+H IV or PH FDC SC treatment must receive a loading dose before continuing with maintenance doses for subsequent administrations. The loading dose should be administered over approximately 8 minutes. Participants should be monitored for at least 30 minutes after a loading dose or after their first PH FDC SC dose administration to observe for injection-related symptoms.

The maintenance dose should be administered over approximately 5 minutes. If the prior injection is well tolerated, participants will be observed for at least 15 minutes for subsequent injections. Participants can be observed for longer periods at the discretion of the healthcare provider (i.e., mobile healthcare provider) if necessary.

The injection should be slowed or interrupted if the participant experiences injection-related symptoms. Refer to the Mobile Clinical Services Training Manual for more details. Participants who experience injection-related symptoms may be pre-medicated with analgesics and antihistamines for subsequent injections. Dose reductions for toxicity are not permitted.

Appendix 16
Asymptomatic Decline in LVEF: Algorithm for Continuation and Discontinuation of PH FDC SC



LVEF = left ventricular ejection fraction

Participants must have an LVEF ≥ 55% measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) to be eligible for the study.

Appendix 17
Safety Reporting of COVID-19 in Study Participants

The purpose for this guidance is to provide direction to Investigators/Study Coordinators about reporting events experienced by trial subjects diagnosed with coronavirus disease (COVID-19) or who may be at risk for developing COVID-19 due to recent travel or possible exposure to someone with COVID-19.

For any Adverse Events, the subjects should be reminded to seek medical care at the nearest hospital or medical clinic. However, if subjects experience the following symptoms, fever, cough or difficulty breathing, they should contact their healthcare profession or other medical advice services and follow local/national guidance in order to limit possible exposure to COVID-19.

When reporting cases of COVID-19:

- **Any cases of confirmed/suspected COVID-19 infections should follow the general Adverse Event (AE) reporting requirements defined in the protocol.**
  - While unavoidable changes in dose or schedule due to COVID-19 need to be captured as protocol deviations, these do not need to be reported as AEs. Changes in dosing or visit schedule are not considered medication errors or misuse.
- For any confirmed/suspected cases, the Investigators are responsible for assessing if an event should be reported as a Serious Adverse Event (SAE) using their clinical judgement and referencing protocol- specific definitions. All SAEs should be reported to the Sponsor per the protocol-required timeline (i.e., within 24 hours).
- The event term should be reported as a diagnosis and not symptoms, such as COVID-19 infection or Coronavirus infection. Test results, Coronavirus test positive or Coronavirus test negative, can also be reported. Should a definitive diagnosis not be possible, 'suspected COVID-19 infection' may be reporting initially. Please provide a diagnosis confirmation once additional information has been obtained. Please consider if the diagnosis meets the criteria of being a significant medical event.
- Complications from the virus infection should follow the reporting guidelines in the study protocol, detailed in the section "Adverse Events That Are Secondary to Other Events" (Section A2–7.3). 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 electronic form or paper reporting form. Please see this section in the protocol for examples.
- For confirmed cases, provide the method by which diagnosis was provided in the "Additional Case Details" section of the AE electronic form or paper reporting form.
  - Was the diagnosis confirmed by a laboratory test ordered by a physician or public health department?
  - Was the diagnosis based on clinical symptoms and history of travel or exposure?

- For all cases, please provide as much detail as available in the "Additional Case Details" section of the AE electronic form or paper reporting form.
    - Contact/travel history during the 14 days prior to symptom onset
    - Clinical signs/symptoms (fever, cough, shortness of breath or other acute respiratory symptoms)
    - Radiology exam (chest CT scan or X-rays)
    - Hematology tests, such as a real-time reverse transcription polymerase chain reaction (rRT- PCR) or serological testing (IgM or IgG detection via enzyme-linked immunoassay, ELISA). Please include the results if positive or negative.
    - If hospitalized, please provide details about the hospitalization course, such as if and how long mechanical ventilation may have been needed.
- Provide treatment details as per usual electronic form reporting processes.
- **Assessing Severity:** When assessing the severity of the event, please use the grading scale referenced in the study protocol. Refer to the section "Assessment of Severity" (Section A2–3.2) in the study protocol for the specific grading scale used. Below are two examples:

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]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to 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, per the definition of serious adverse event see the study protocol.

[d] Grade 4 and 5 events must be reported as serious adverse events, per the definition of serious adverse event see the study protocol.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Notes: Developed by the Division of Microbiology and Infectious Diseases.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event in the study protocol.

Appendix 18
Assessments for Participants who Require Additional Cycles of P+H IV or PH FDC SC Due to a Delay With Surgery

The following assessments should be conducted for participants who require additional cycles of P+H IV or PH FDC SC due to a delay with surgery (see Section 4.1.1).

	Assessments at each additional cycle
Limited physical examination [a] [b]	x
Vital signs [a] [c]	x
Weight [a] [d]	x
Clinical tumor assessment / breast examination [a] [e]	x
Hematology / limited biochemistry [f]	x
Treatment (P+H IV or PH FDC SC)	x
Adverse events [g]	x
Concomitant medication [h]	x

a Assessment may be done within 3 days prior to the treatment day.

b Limited physical examinations are symptom-directed and, in addition to the scheduled examinations indicated, may be conducted by a mobile HCP as clinically indicated. New or worsened clinically significant abnormalities observed post-baseline should be recorded as AEs on the Adverse Event electronic form. After the End of Treatment, physical examinations should be conducted by treating physician in accordance with institutional practice or the American Cancer Society/American Society of Clinical Oncology Breast Cancer (ACS/ASCO) Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016).

c Vital signs (respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated position, and temperature) will be taken before the administration of study treatment and before and after P+H IV/PH FDC SC injection.

d Weight will be measured during screening and on Day 1 of each cycle. If variation of ± 10% occurs, as compared with baseline, the trastuzumab IV and chemotherapy doses will be recalculated.

e Performed by clinical breast examination (mandatory) and other methods of evaluation as per routine clinical practice.

f Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN. During the treatment period, bloods for hematology / biochemistry may be taken within three days prior to study treatment administration.

g After initiation of study drugs, all adverse events will be reported until 28 days after the last 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 $treatment$ (see Appendix 2).

h All concomitant medications used by the participant from 7 days prior to initiation of study drug until the End of Treatment Visit will be reported.

Reference

Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol 2016;34:611–35.

Appendix 19
Assessments for Participants from Arm E who Discontinue Trastuzumab Emtansine (Due to Intolerance) and who Switch to PH FDC SC

Participants in Arm E who discontinue trastuzumab emtansine (due to intolerance) can be discontinued from the study (and be treated as per standard of care) or can remain in the study and be treated with PH FDC SC in the hospital as to complete 14 cycles of HER2-directed adjuvant study treatment in total. This decision is at the discretion of the treating physician.

Assessment	**Timing During Adjuvant Phase** [a]	**Treatment Completion/ Discontinuation** [b]	**F/U (6–9 mo post last dose)**
Complete physical examination [c] [d]	Last cycle	x	
Limited physical examination [c] [e]	Every cycle but the last cycle		
Vital signs [c] [f]	Every cycle	x	
ECOG performance status [c] [g]	Cycles 1, 3, 6, 9, and last cycle	x	
Weight [c]	Every cycle	x	
Clinical breast examination [c] [h]	Cycle 1, 5, 9 and last cycle	x	
Bilateral mammogram (or another imaging method as, per local practice) [i]		x	
LVEF (ECHO or MUGA) [j]	Cycle 1, 5, 9 and last cycle	x	
Pregnancy test [k]	Cycle 1, 5, 9 and last cycle	x	x
Hematology / limited biochemistry [l]	Every cycle	x	
PH FDC SC (q3w) [m]	Every cycle		
EORTC QLQ-C30 [n] – Appendix 8	Cycle 7 and 14		
Adverse events [o]	Continuous	x	x
Concomitant medication [p]	Continuous	x	

ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition (scan).

Note: Unless otherwise specified, assessments should be performed within three days of the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. For all protocol-mandated study visits, a time window of ± 3 days is allowed. If a protocol mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date. Unscheduled visits may be performed if clinically indicated. The following assessments should be performed at a minimum: concomitant medications, adverse events, and vital signs. Additional assessments may be performed as clinically indicated, per investigator discretion.

a Treatment will be given so that in total, 14 cycles of HER2-directed therapy (trastuzumab emtansine or PH FDC SC) are administered in the adjuvant setting. Cycle numbers represent a continuation of the adjuvant treatment phase cycle numbers (Table 4).

b Treatment completion or discontinuation visits will optimally be scheduled for 28 (± 7 days) following the last dose of study medication and will include all evaluations scheduled for the final visit.

c Assessment may be done within 3 days prior to the treatment day.

d Complete physical examinations should include physical measurements (body weight in kilograms and height in centimeters) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

e Limited physical examinations are symptom-directed and, in addition to the scheduled examinations indicated, may be conducted by a mobile HCP as clinically indicated. Physical examinations may be physician-guided remotely with the HCP assisting in the participant's home. New or worsened clinically significant abnormalities observed post-baseline should be recorded as AEs on the Adverse Event electronic form. After the End of Treatment, physical examinations should be conducted by treating physician in accordance with institutional practice or the American Cancer Society/American Society of Clinical Oncology Breast Cancer (ACS/ASCO) Breast Cancer Survivorship Care Guideline (Runowicz et al. 2016).

f Vital signs (respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated position, and temperature) will be taken before and after PH FDC SC injection.

g ECOG Performance Status should be assessed by the HCP at least every 3–4 months during the adjuvant treatment period and at the treatment completion or discontinuation visit.

h During the adjuvant treatment period, clinical breast examination should be performed to detect signs of locoregional relapse at least every 3–4 months (Cycle 1, Cycle 5, Cycle 9 and last cycle) and at the treatment completion or discontinuation visit.

i The mammogram at the treatment completion or discontinuation visit can be replaced by other conventional imaging methods such as MRI or ultrasound as per local medical practice, at the investigator's discretion, but the same method of assessment must be used throughout for an individual participant. If a mammogram has been conducted as part of routine preventive care within 4 months of the treatment completion or discontinuation visit, it may be used in lieu of the end of study mammogram.

j For participants whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each participant and is preferably performed and assessed by the same assessor. *All LVEF assessments will be performed during Days 15–21 of 3-week cycles prior to the cycle indicated, LVEF assessment may also be performed on Day 1 of treatment. Results of LVEF assessments must be available before treatment is administered and according to the scheduled timepoints. Apart from the specified mandatory LVEF assessment, the investigator may request additional assessment based on the individual participant's cardiovascular function with a minimum frequency of 3–4 months.*

k All female participants of childbearing potential (refer to Section 5.1.1 for definition) will have a urine pregnancy test at cycle 1, 5 or 6, 9, and last cycle during adjuvant phase; as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. Pregnancy test at 7 months (i.e., between 6–9 months follow-up) can be performed if indicated. Note that participants are required to continue contraception for 7 months after study treatment is complete.

l Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN. During the treatment period, bloods for hematology / biochemistry may be taken within three days prior to study treatment administration.

m PH FDC SC should not be initiated within < 3 weeks from last dose of trastuzumab emtansine. All participants receive maintenance dose of 600 mg pertuzumab and 600 mg trastuzumab. Participants who have had ≥ 6 weeks since their last trastuzumab emtansine treatment must receive a PH FDC SC loading dose before continuing with maintenance doses for subsequent administrations.

n Completed before treatment is administered on Day 1 of the indicated treatment cycles.

o After initiation of study drugs, all adverse events will be reported until 28 days after the last 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 *treatment* (see Appendix 2).

p All concomitant medications used by the participant from 7 days prior to initiation of study drug until the End of Treatment Visit will be reported.

Appendix 20
Investigational and Auxiliary Medicinal Product Designations (for Use in European Economic Area)

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
PH FDC SC (RO7198574)	*IMP (test product)*	*Approved*	*Yes*
Pertuzumab (RO4368451)	*IMP (test product)*	*Approved*	*Yes*
Trastuzumab (RO45-2317)	*IMP (test product)*	*Approved*	*Yes*
Trastuzumab emtansine (RO5304020)	*IMP (test product)*	*Approved*	*Yes*
Docetaxel	*AxMP (background therapy)*	*Approved*	*Yes*
Carboplatin	*AxMP (background therapy)*	*Approved*	*Yes*
Doxorubicin	*AxMP (background therapy)*	*Approved*	*Yes*
Paclitaxel	*AxMP (background therapy)*	*Approved*	*Yes*
Cyclophosphamide	*AxMP (background therapy)*	*Approved*	*Yes*
Endocrine therapy	*AxMP (background therapy)*	*Approved*	*Yes*
Premedications	*AxMP (other)*	*Approved*	*Yes*
Diphenhydramine	*AxMP (rescue medication)*	*Approved*	*Yes*
Solu-Cortef	*AxMP (rescue medication)*	*Approved*	*Yes*
Epinephrine	*AxMP (rescue medication)*	*Approved*	*Yes*

AxMP =auxiliary medicinal product; EEA □ European Economic Area; IMP =investigational medicinal product.

Appendix 21
Abbreviations

Abbreviation or Term	Definition
AC	Doxorubicin plus cyclophosphamide
ACE	Angiotensin-converting enzyme
ACS/ASCO	American Cancer Society/American Society of Clinical Oncology Breast Cancer
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALND	Axillary lymph node dissection
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARR	Administration-related reactions
AST	Aspartate aminotransferase
AV	Atrioventricular
AxMP	*Auxiliary medicinal product*
CAP	College of American Pathologists
CHF	Congestive heart failure
CI	Confidence interval
ClinRO	Clinician-reported outcome
CMF	Concomitant medications form
COVID-19	Coronavirus disease 2019
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
DCIS	Ductal carcinoma in situ
ddAC	Dose-dense doxorubicin plus cyclophosphamide
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EMEA	European medicines agency
EORTC QLQ-30	European Organization for Research and Treatment of Cancer core quality of life questionnaire

Appendix 21: Abbreviations

Abbreviation or Term	Definition
ER	Estrogen receptor
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBV/HCV	Hepatitis B/C Virus
HCP	Healthcare professional
HCPQ	Healthcare professional questionnaires
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IM	Intramuscular
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational new drug (application)
INR	International normalized ratio
IRB	Institutional review board
ISH	*In situ* hybridization
ITT	Intention-to-treat
IV	Intravenous
IxRS	Interactive voice or web-based response system
LCIS	Lobular carcinoma in situ
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
mITT	Modified intention-to-treat
MRI	Magnetic resonance imaging
MUGA	Multiple-gated acquisition (scan)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York heart association

Appendix 21: Abbreviations

Abbreviation or Term	Definition
P+H IV	IV administration of pertuzumab and trastuzumab
pCR	Pathologic complete response
PgR	Progesterone receptor
PH FDC SC	Pertuzumab and trastuzumab fixed-dose combination for subcutaneous use
PK	Pharmacokinetic
PPQ	Patient preference questionnaire
PRO	*Patient*-reported outcome
q2w	Every 2 weeks
q3w	Every 3 weeks
QTcF	QT interval corrected through use of Fridericia's formula
RBC	Red blood cell
rhTPO	Recombinant thrombopoeitin
rHuPH20	Recombinant human PH20 hyaluronidase
SAE	Serious adverse event;
SC	Subcutaneous
SLNB	Sentinel lymph node biopsy
TCb	docetaxel and carboplatin
TM	Trademark
ULN	Upper limit of normal
WBC	White blood cell
β-HCG	Beta human chorionic gonadotropin

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