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: Statistical Analysis Plan Version 2: 11-Apr-2025

STATISTICAL ANALYSIS PLAN

STUDY 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**
STUDY NUMBER:	MO43110
STUDY NAME:	ProHer
VERSION NUMBER:	2.0
ROCHE COMPOUND(S):	Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous (PH FDC SC) administration (RO7198574) Pertuzumab IV (RO4368451) Trastuzumab IV (RO0452317) Trastuzumab emtansine IV (RO5304020)
EUDRACT NUMBER:	2021-002346-33

STATISTICAL ANALYSIS PLAN APPROVAL

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SPONSOR:	F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS:	Grenzacherstrasse 124 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp on the last page of this document

IND NUMBER:	Not applicable
NCT NUMBER:	NCT05415215
PLAN PREPARED BY:	[redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

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SPONSOR:	F. Hoffmann-La Roche Ltd
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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on Roche SAP model document v2.0 (28Feb2022).

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
2.0	see electronic date stamp on the last page of this document	V 3.0, 25 January 2024
1.0	31 July 2024	V 3.0, 25 January 2024

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Keys changes to the SAP, along with the rationale(s) for each change, are summarized below.

Section	Description of Change	Rationale for Change
3	Adjuvant cross-over modified Intention-to-Treat analysis set (mITTcross) has been updated to exclude patients who didn't complete the radiotherapy before entering the Cross-Over period.	As per protocol, the primary endpoint of this study is to evaluate patient preference for PH FDC SC administration in the home setting during the cross-over period of the adjuvant phase. This endpoint will be assessed through Question 1 of the PPQ. According to protocol, the primary endpoint will be analyzed using the Adjuvant Cross-over Modified Intention-to-Treat Analysis Set (mITTcross). The mITTcross is currently defined as 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 (i.e., non-missing answer for patient who received at least one dose of PH FDC SC in the home setting). Participants will be included in the analyses according to the treatment sequence they were assigned. The rationale for employing a randomized cross-over design in this study was to reduce bias and confounding factors in the process of participant assignment. Stratified randomization can prevent confounding factors in the interpretation of study endpoints caused by known factors such as disease stage, neoadjuvant chemotherapy, and type of surgery. During the course of the study, it was noted that some patients were randomized into the cross-over period without finalizing their radiotherapy treatment (this is a major protocol deviation), which must be completed before entering the cross-over period as stated in the protocol. Radiotherapy was not considered as part of the stratification criteria.

		Therefore, it is necessary to amend the mITTcross analysis set description to clearly state that participants who didn't complete the radiotherapy before the start of the cross-over period will not be considered as part of the mIIT cross-analysis set. This amendment will ensure the integrity of the study endpoints and provide more accurate and reliable results.
4.2.3.2	The sensitivity analysis of the primary endpoint excluding patients who received radiotherapy after the start of the cross-over period has been removed.	Patients who received radiotherapy after the start of the cross-over period are now excluding from the mITTcross analysis set; therefore, the sensitivity analysis excluding these patients now becomes the main analysis of the primary endpoint.
4.3.3	Subgroup analysis of the proportion of participants with pCR by Hormone Receptor status (HR) added.	In FEDERICA study, HR+ patients had lower pCR rates than HR-.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
EORTC QLQ-30	European Organization for Research and Treatment of Cancer core quality of life questionnaire
HCP	healthcare professional
HCPQ	Healthcare Professional Questionnaire
HER2	human epidermal growth factor receptor 2
HER2+	HER2-positive
HRQoL	Health-related quality of life
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
P+H IV	IV administration of pertuzumab and trastuzumab
pCR	pathologic complete response
PH FDC SC	pertuzumab and trastuzumab fixed-dose combination for subcutaneous use
PPQ	Patient Preference Questionnaire
PRO	patient-reported outcomes
Q2w	every 2 weeks
Q3w	every 3 weeks
SAE	serious adverse events
SAP	Statistical Analysis Plan
ULN	upper limit of normal

1. INTRODUCTION

The analyses described in this statistical analysis plan (SAP) will supersede those specified in Protocol MO43110 for the purposes of a regulatory filing.

This SAP provides details of the planned analyses and statistical methods for Study MO43110, a phase IIIb, multinational, multicenter, randomized, open-label study to evaluate the patient preference of pertuzumab and trastuzumab fixed-dose combination for subcutaneous use (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-positive (HER2+) breast cancer.

1.1 OBJECTIVES AND ENDPOINTS

Table 1 Primary Objective and Corresponding Endpoint

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). Question 1 of the PPQ is as follows: “All things considered, which setting for your treatment did you prefer?” and the possible responses are: “Hospital”, “Home” or “No preference”.

PH FDC SC = pertuzumab and trastuzumab fixed-dose combination for subcutaneous use; PPQ = Patient Preference Questionnaire

Table 2 Secondary Objectives and Endpoints

Secondary Objectives	Corresponding Endpoints
• To evaluate the perception of healthcare professionals (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
• To collect pathological 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
• 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

• 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
• 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
• 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 • 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 • 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 • 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; AJCC = American Joint Committee on Cancer; EORTC QLQ-30 = European Organization for Research and Treatment of Cancer core quality of life questionnaire; HCP = healthcare professional; HCPQ = Healthcare Professional Questionnaire; HRQoL = health-related quality of life; IV = intravenous; LVEF = left ventricular ejection fraction; P+H = pertuzumab and trastuzumab; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; pCR = pathologic complete response; PH FDC SC = pertuzumab and trastuzumab fixed-dose combination for subcutaneous use; SAE = serious adverse event.

1.2 STUDY 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 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.

- **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, with a loading dose [840 mg pertuzumab and 8 mg/kg trastuzumab] in first cycle, followed by maintenance doses [420 mg pertuzumab and 6 mg/kg trastuzumab].
- **Arm B:** PH FDC SC q3w plus chemotherapy (standard regimen) in the hospital, with a loading dose [1200 mg pertuzumab and 600 mg trastuzumab] in first cycle, followed by maintenance doses [600 mg pertuzumab and 600 mg trastuzumab].

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;
- **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;
- **Option 3:** Dose-dense doxorubicin (60 mg/m²) plus cyclophosphamide (600 mg/m²) every 2 weeks (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.

Randomization will be stratified by disease stage at screening (operable, locally advanced, or inflammatory, as defined in Section **Error! Reference source not found.**) and neoadjuvant chemotherapy option (anthracycline-free or anthracycline-based, as defined in Section **Error! Reference source not found.**).

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). 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.

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.

- **Adjuvant Phase**

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.

After surgery, radiotherapy is to be given as clinically indicated and 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).

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 (operable, locally advanced, or inflammatory, as defined in Section **Error! Reference source not found.**), type of surgery (conservative or mastectomy), and neoadjuvant chemotherapy option (anthracycline-free or anthracycline-based, as defined in Section **Error! Reference source not found.**).

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), 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.

<u>Participants who have residual disease after surgery</u>

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. 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.

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.

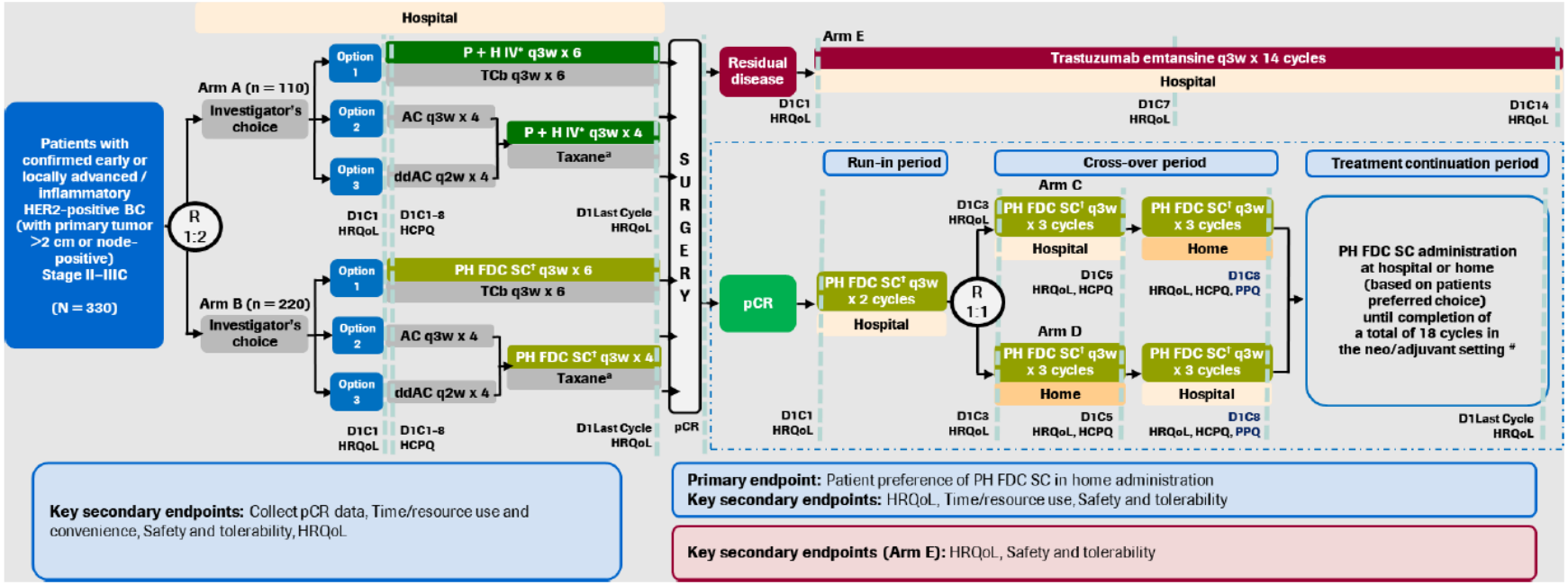
Radiotherapy should be given as clinically indicated and the timing to start the radiotherapy should be based on the local practices, but it must start within 6 weeks after surgery.

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.
Figure 1 presents an overview of the study design.

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.

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.
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 but must be performed ≤ 6 weeks the last systemic neoadjuvant therapy after.
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 can be administered at the investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab.

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.

1.2.1 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 interactive voice or web-based response system (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 1.2). Randomization in the neoadjuvant phase will be stratified by disease stage at screening (operable, locally advanced or inflammatory) and neoadjuvant chemotherapy option (anthracycline-free [chemotherapy option 1] or anthracycline-based [chemotherapy options 2 or 3]; see Section 1.2).

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). 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 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 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) 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 1.2.

1.2.2 Independent Review Facility

No Independent Review Facility (IRF) is planned for this study.

1.2.3 Data Monitoring

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.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

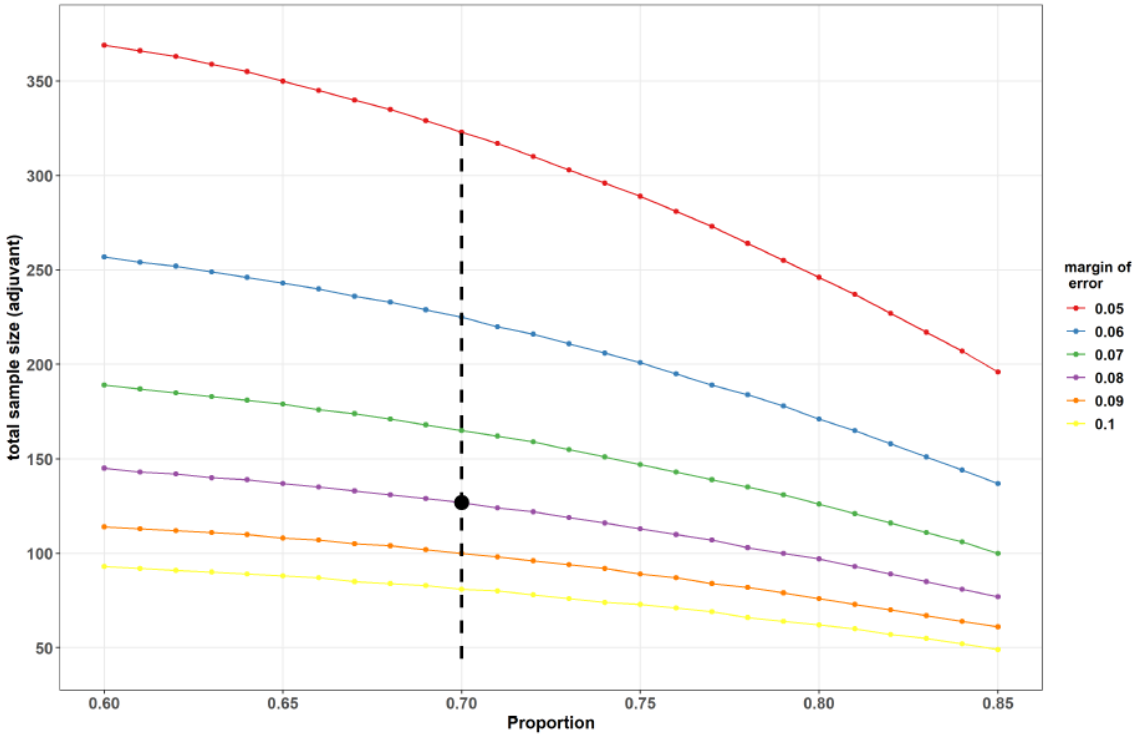
The primary endpoint of this study is the proportion of participants who prefer PH FDC SC administered by an HCP in the home setting compared with the hospital setting during the adjuvant phase. No formal statistical hypotheses will be tested for this study.

2.2 SAMPLE SIZE DETERMINATION

Approximately 330 participants will be enrolled for the neoadjuvant phase of study treatment such that approximately 150 evaluable participants enter Arms 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 Arms 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.

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



3. ANALYSIS SETS

Table 3 Participant Analysis Sets

Participant Analysis Set	Description
Neoadjuvant safety analysis set (SASab)	All participants randomly assigned to study treatment and receiving at least one planned study treatment in the neoadjuvant phase. Participants will be included in the analyses according to the treatment that they actually received.
Neoadjuvant full analysis set (FASab)	All participants randomly assigned to study treatment, whether or not they received treatment. Participants will be included in the analyses according to the treatment that they were assigned.
Adjuvant safety analysis set for PH FDC SC cohort (SAScd+)	All participants with pCR entering the PH FDC SC cohort in the adjuvant phase and receiving at least one dose of PH FDC SC. Participants will be included in the analyses according to the treatment that they actually received.
Adjuvant full analysis set for PH FDC SC cohort (FAScd+)	All participants with pCR entering the PH FDC SC cohort in the adjuvant phase and receiving at least one dose of PH FDC SC. Participants will be included in the analyses according to the treatment that they were assigned.

Participant Analysis Set	Description
Adjuvant safety analysis set for trastuzumab emtansine IV cohort (SASe)	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.
Adjuvant cross-over Intention-to-Treat analysis set (ITTcross)	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. Participants will be included in the analyses according to the treatment sequence they were assigned.
Adjuvant cross-over modified Intention-to-Treat analysis set (mITTcross)	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 (i.e., non-missing answer for patient who received at least one dose of PH FDC SC in the home setting) and having completed the radiotherapy before entering the Cross-Over period. Participants will be included in the analyses according to the treatment sequence they were assigned.
Adjuvant cross-over safety analysis set (SAScross)	All participants randomly assigned into the cross-over period and receiving at least one PH FDC SC treatment in the cross-over period. Participants will be included in the analyses according to the treatment setting that they actually received.

4. STATISTICAL ANALYSES

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.

In this study, there are 2 treatment phases that will be analyzed separately: the neoadjuvant phase and the treatment phase. Within the neoadjuvant and adjuvant phases, different periods are defined for the analysis.

- The **neoadjuvant phase** will consist of:
    - The **neoadjuvant treatment phase** will consist of 6 or 8 planned cycles of HER2-targeted therapy (PH FDC SC or P+H IV) plus chemotherapy in the hospital setting (the number of cycles being defined by the chemotherapy option chosen), followed by a surgery. If surgery is delayed, a maximum of two additional cycles of HER2-targeted therapy can be administered before surgery. The neoadjuvant phase will be defined as the time between the start of first dose of study treatment in the neoadjuvant phase and the surgery date, if any, or the study completion/discontinuation date otherwise.

- The **surgery phase** will be defined as the time between the surgery date and the start of first dose of study treatment in the adjuvant phase, if any, or the study completion/discontinuation date otherwise.

- The **adjuvant phase** will consist of:

  - **PH FDC SC cohor**t: for participants who have achieved pCR after surgery, the adjuvant phase will consist of 3 periods:

    - **Run-in period:** 2 planned cycles (plus 1 optional cycle in case the radiotherapy is delayed) of PH FDC SC in the hospital setting. Randomization will occur after completion of the last cycle of radiotherapy and last cycle of PH FDC SC during the run-in period. For participants with pCR entering the adjuvant phase, the run-in period will be defined as the time between the start of first dose of PH FDC SC in the adjuvant phase and the start of first dose of PH FDC SC occurring after the randomization in the adjuvant phase (i.e., after completion of run-in), if any, or the study completion/discontinuation date otherwise.

    - **Cross-over period:** 3 cycles of PH FDC SC in the hospital setting followed by 3 cycles of PH FDC SC in the home setting, or vice versa 3 cycles of PH FDC SC in the home setting followed by 3 cycles of PH FDC SC in the hospital setting. The cross-over period starts immediately after completion of the run-in period. For participants randomized in the adjuvant phase, the cross-over period will be defined as the time between the start of the first dose of PH FDC SC occurring after the randomization in the adjuvant phase and the start of the first dose of PH FDC SC after PPQ completion, if any, or the study completion/discontinuation date otherwise.

    - **Treatment continuation period:** following completion of the cross-over period, patients will enter the treatment continuation period wherein they will receive the remaining anti-HER2 treatment cycles (PH FDC SC either in the home or in the hospital setting as selected by the patient at the end of cross-over period) required to complete their 18 planned cycles. The treatment continuation period will be defined as the time between the start of the first dose of PH FDC SC after completion of the PPQ and the date of the last dose received plus 28 days or the study completion/discontinuation date, whichever occurs first.

  - **Trastuzumab emtansine arm:** for participants with residual disease following completion of neoadjuvant therapy and surgery, the adjuvant phase

will consist of 14 cycles of trastuzumab emtansine IV at hospital. The adjuvant phase will be defined as the time between the start of first dose of trastuzumab emtansine in the adjuvant phase and the date of the last dose received plus 28 days or the study completion/discontinuation date, whichever occurs first.

- The **follow-up period** will be defined as the time between the last dose received plus 28 days and the study completion/discontinuation date.

A general rule for baseline measurement is the last available measurement before the first administration of study drug for the corresponding study phase/period.

Neoadjuvant safety analysis set (SASab) is used for the safety analysis in the neoadjuvant phase.

Neoadjuvant full analysis set (FASab) is used for the analysis of pCR and clinical outcome assessments (HCPQ and HRQoL) in the neoadjuvant phase.

Adjuvant safety analysis set for PH FDC SC cohort (SAScd+) is used for the analysis of safety of the PH FDC SC cohort in the entire adjuvant phase.

Adjuvant full analysis set for PH FDC SC cohort (FAScd+) is used for the analysis of HRQoL and other clinical outcome assessments of the PH FDC SC cohort in the entire adjuvant phase.

Adjuvant safety analysis set for trastuzumab emtansine IV cohort (SASe) is used for the analysis of safety and HRQoL in the trastuzumab emtansine IV arm.

Adjuvant cross-over modified Intention-to-Treat analysis set (mITTcross) is used for the analysis of the primary endpoint and HCPQ in the crossover period.

Adjuvant cross-over Intention-to-Treat analysis set (ITTcross) is used for the analysis of the primary endpoint and HCPQ in the crossover period as a sensitivity analysis.

Adjuvant cross-over safety analysis set (SAScross) is used for the safety analysis in the cross-over period.

4.2 PRIMARY ENDPOINT

4.2.1 Definition of Primary Endpoint

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 1.1 of SAP (see Primary Objective in Table 1).

The primary endpoint will be assessed through Question 1 of PPQ: “All things considered, which setting for your treatment did you prefer?”. The PPQ will be completed by the participants in Arm C and D who have entered the cross-over period of the study. The PPQ will be completed on Day 1 of the last cycle of the cross-over period. 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 patient preference will be analyzed on the mITTcross by treatment setting sequence and overall. Patients without a valid response to Question 1 of the PPQ i.e., patients who discontinued study treatment without receiving at least one dose of PH FDC SC in the home setting or died before they answered PPQ, will not be included in the analysis.

4.2.2 Main Analytical Approach for Primary Endpoint(s)

Patient preference will be summarized by presenting the number and percentage of patients in each category (Home, Hospital and No preference). A point estimate will be calculated with associated 95% exact Clopper–Pearson CI for the proportion of participants who prefer PH FDC SC administered by HCP in the home setting and will be described by treatment setting sequence and overall.

4.2.3 Supplementary Analysis

4.2.3.1 Subgroup Analyses for Primary Endpoint

Patient preference will also be summarized descriptively by stratification factors: disease stage at screening (operable, locally advanced, inflammatory), type of surgery (conservative, mastectomy) and neoadjuvant chemotherapy option (anthracycline-free, anthracycline-based), by presenting the number and proportion of patients in each category (Home, Hospital and No preference), as well as the 95% exact Clopper–Pearson CI for the proportion of participants who prefer PH FDC SC administered by HCP in the home setting, on the mITTcross.

Exploratory subgroup analyses will also be performed on the mITTcross by:

- Age (<65 years vs. >= 65 years)
- Race
- Clinical stage at presentation (II-IIIA vs. IIIB-IIIC)
- Country

4.2.3.2 Sensitivity Analyses for Primary Endpoint

On ITTcross analysis set

The analysis of the primary endpoint (see Section **Error! Reference source not found.**) will be repeated on the ITTcross as a sensitivity analysis.

The analysis will be similar to the main analysis, except that it will include patients with missing data for the Question 1 of PPQ like, for example, patients who entered the

adjuvant cross-over period but early discontinued from study treatment without receiving at least one dose of PH FDC SC in the home setting.

Missing answers for Question 1 of PPQ will be considered as not preferring administration in the home setting.

Excluding patients who do not fully comply with the protocol during the run-in and cross-over periods

The analysis of the primary endpoint (see Section 4.2.2) will be repeated as a sensitivity analysis on a subset of the mITTcross excluding patients:

- who received radiotherapy after the start of the cross-over period
- who received more than 3 run-in cycles
- who did not receive 3 cycles at home followed by 3 cycles at hospital, or vice-versa, during the cross-over period.

In patients with at least one Grade >= 3 Adverse Event

The analysis of the primary endpoint (see Section 4.2.2) will be repeated as a sensitivity analysis on a subset of the mITTcross including only patients with at least one grade >=3 adverse event at any time (neoadjuvant or adjuvant phases) before the PPQ completion.

4.3 SECONDARY ENDPOINTS

4.3.1 Healthcare Professional Questionnaire (HCPQ) – Neoadjuvant Phase

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 will be assessed by summarizing responses to individual questions of the HCPQ collected in the neoadjuvant phase using the FASab, by study treatment and overall.

HCPQ- Neoadjuvant Phase Drug Preparation Area

The number of HCPQs completed and the specialties of healthcare professional respondents (Pharmacist/Pharmacy Technician, Nurse, Other) will be summarized overall.

Experience with PH FDC SC and P+H IV infusion dispensing and preparation

Response to the question 1b “How long did it take to prepare the treatment for use?” will be summarized by cycle and stratified by route of drug administration (question 1a).

Response to the question 1b “How long did it take to prepare the treatment for use?” will also be summarized by cycle and stratified by route of drug administration (question 1a) for each healthcare professional specialty and each individual country.

Impact on Clinical Management and Clinical Efficiency

Responses to individual questions 2 to 4 will be summarized overall, by healthcare professional specialty and by individual country.

HCPQ - Neoadjuvant Phase Administering Treatment

The number of HCPQs completed and the specialties of Healthcare Professional Respondents (Nurse, Treating Doctor, Other) will be summarized overall.

Experience with PH FDC SC injection and P+H IV infusion administration

Responses to individual questions 1b to 1g will be summarized by cycle and stratified by route of drug administration (question 1a).

Responses to individual questions 1b to 1g will also be summarized by cycle and stratified by route of drug administration for each healthcare professional specialty and each individual country.

Impact on Clinical Management and Clinical Efficiency

Responses to individual questions 2 to 11 will be summarized overall, by healthcare professional specialty and by individual country.

4.3.2 Healthcare Professional Questionnaire (HCPQ) – Adjuvant Cross-Over Period

In the same manner, the perception of HCPs of time/resource use of PH FDC SC at home compared to hospital during the adjuvant cross-over period will be assessed by summarizing responses to individual questions of the HCPQ collected during the cross-over period using the mITTcross, by treatment setting sequence and overall. The analysis will be repeated on the ITTcross.

HCPQ - Adjuvant Phase Drug Preparation Area

The number of HCPQs completed and the specialties of healthcare professional respondents (Pharmacist/Pharmacy Technician, Nurse, Other) will be summarized overall.

Experience with PH FDC SC preparation

Responses to individual questions 1a to 1c will be summarized by cycle and stratified by setting of administration.

Responses to individual questions 1a to 1c will also be summarized by cycle and stratified by setting of administration for each healthcare professional specialty and each individual country.

Impact on Clinical Management and Clinical Efficiency

Responses to individual questions 2 to 4 will be summarized overall, by healthcare professional specialty and by individual country.

HCPQ - Adjuvant Phase Administering Treatment

The number of HCPQs completed and the specialties of Healthcare Professional Respondents (Nurse, Treating Doctor, Other) will be summarized overall.

Experience with PH FDC SC injection at hospital and at home

Responses to individual questions 1a to 1l will be summarized by cycle and stratified by setting of administration.

Responses to individual questions 1a to 1l will also be summarized by cycle and stratified by setting of administration for each healthcare professional specialty and each individual country.

Impact on Clinical Management and Clinical Efficiency

Responses to individual questions 2 to 7 will be summarized overall, by healthcare professional specialty and by individual country.

4.3.3 Pathologic Complete Response (pCR)

Proportion of participants achieving pCR, is defined as the proportion of participants with 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 (i.e., ypT0/Tis ypN0) after surgery, according to local pathologist assessment following the AJCC criteria (FDA 2020).

The proportion of participants with pCR will be summarized for the FASab, by study treatment and overall.

The proportion of participants with pCR will also be summarized for the FASab by disease stage at screening (operable, locally advanced, inflammatory), clinical stage at presentation (II-IIIA vs. IIIB-IIIC), neoadjuvant chemotherapy regimen (options 1, 2 and 3 for arm A and arm B, see section 1.2), number of neoadjuvant PH cycles received (< 4 cycles vs. ≥4 cycles) and Hormone Receptor status (Positive (ER and/or PgR positive) vs. Negative (ER and PgR negative) vs. Unknown).

4.3.4 EORTC QLQ-C30

HRQoL, as measured by EORTC QLQ-C30 scores including change from baseline, will be summarized by visit, separately for:

- the neoadjuvant phase using the FASab, by study treatment and overall;
- for PH FDC SC cohort in the adjuvant phase using the FAScd+, by treatment setting sequence and overall;
- and for the trastuzumab emtansine arm in the adjuvant phase using the SASe.

Summary statistics (mean, standard deviation, median, and range) of linearly transformed absolute scores and mean changes from baseline will be calculated for all items and subscales (treatment-related symptoms and function, Global Health Status/HRQoL) of the EORTC QLQ-C30 at each assessment timepoint for each treatment arm.

The EORTC QLQ-C30 data will be scored according to the EORTC scoring manual (Fayers 2001). Missing data will be reported by timepoint. In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

EORTC QLQ-C30 completion rates and reasons for missing data will be summarized at each timepoint.

In addition, summary statistics of linearly transformed absolute scores by visit during the cross-over period will be produced, using the ITTcross, by treatment setting.

4.4 EXPLORATORY ENDPOINTS ANALYSIS

4.4.1 Patient's Choice of Setting for the Treatment Continuation Period

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 summarized for the ITTcross, by treatment setting sequence and overall.

A consistency table with answer to question 1 of the PPQ will also be provided. For each patient's preference category as per the question 1 of the PPQ (Home, Hospital and No preference), the number and percentage of patients who select each treatment administration setting for the Treatment Continuation Period (Home, Hospital) will be summarized.

4.4.2 Patient Preference Questionnaire (Questions 2 and 3)

For patients who reported a preference for one of the two administration settings in question 1 of the PPQ, the strength of their preference (very strong, fairly strong, not very strong) and the two main reasons for their preference will be summarized with the number and proportion of responses for each category of preference (Home and Hospital) on the mITTcross and the ITTcross by treatment setting sequence and overall.

A listing of the two main reasons for their preference and any other comments patients added about their preference will be provided.

4.5 SAFETY ANALYSES

Safety analyses for neoadjuvant and adjuvant phase will be conducted separately. For the adjuvant phase, the analysis will be produced separately for the PH FDC SC cohort and for the trastuzumab emtansine IV arm. In addition, safety analyses will also be performed on the cross-over period of the adjuvant phase for the PH FDC SC cohort.

Safety analyses will be produced separately for each study phase/period on the following analysis sets:

- Neoadjuvant phase: neoadjuvant safety analysis set (SASab)
- Adjuvant phase:
    - PH FDC SC cohort: adjuvant safety analysis set for PH FDC SC cohort (SAScd+)
    - trastuzumab emtansine IV arm: adjuvant safety analysis set for trastuzumab emtansine IV cohort (SASe)
    - cross-over period: adjuvant cross-over safety analysis set (SAScross)

4.5.1 Extent of Exposure

For the neoadjuvant phase, study treatment exposure (treatment duration, number of cycles, total dose received and dose delays) will be summarized with descriptive statistic separately for each investigational medicinal product (IMP) (i.e., pertuzumab IV, trastuzumab IV and PH FDC SC) on the SASab.

For the PH FDC SC cohort in the adjuvant phase, study treatment exposure (treatment duration, number of cycles overall, at home and at hospital, total dose received and dose delays) will be summarized with descriptive statistics by period (run-in, cross-over and continuation) and overall on the SAScd+.

For the trastuzumab emtansine IV arm in the adjuvant phase, study treatment exposure (treatment duration, number of cycles, total dose received, dose modifications and dose delays) will be summarized with descriptive statistic on the SASe.

4.5.2 Adverse Events

Verbatim description of adverse events (AEs) will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0). Adverse events will be summarized by MedDRA term, appropriate MedDRA levels (system organ class [SOC] and preferred term [PT]), and when specified by NCI CTCAE grade. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

Analysis of AEs will focus on treatment-emergent AEs (TEAEs), i.e., AEs occurring on or after the day of first study drug administration and on or before the day of last study drug administration + 28 days.

TEAEs will be included in the summary tables.

All AEs will be listed.

AEs starting more than 28 days after the last administration of study treatment will be listed only.

In case of study treatment switch allowed by the protocol (from P+H IV to PH FDC SC in the neoadjuvant phase or from trastuzumab emtansine IV to PH FDC SC in the trastuzumab emtansine IV arm), AE summaries will include data up to the study treatment switch only. If applicable, additional AE summaries will be produced on the subset of patients with treatment switch, on the period after the switch. AEs occurring after a treatment switch will be flagged in the listings.

All AEs, SAEs, AEs leading to death, Grade ≥ 3 AEs, AESIs, AEs related to IMP, AEs related to chemotherapy (for the neoadjuvant phase), AEs leading to IMP discontinuation or study discontinuation, AEs leading to IMP dose modification or interruption, cardiac AEs (including LVEF events) will be summarized. Deaths and cause of death will be summarized.

Incidence of AEs will be summarized separately for each study phase. For the neoadjuvant phase, summaries will be produced by study treatment and chemotherapy option, and overall. For the PH FDC SC cohort in the adjuvant phase, summaries will be produced by period and treatment setting, and overall.

An AE will be assigned to the period/setting corresponding to the last treatment received on or prior the start date of the AE. AEs that started during a period/setting and continued into subsequent period/setting (even if the AE changed severity grade) will be summarized under the period/setting during which it first occurred. These AEs will be flagged in listings. If there is no subsequent period/setting, then the 28-day cut off will be

applied. AEs starting more than 28 days after the last administration of study treatment will be listed only.

Where an AE start date is partially or fully missing, and it is unclear to which treatment period or setting the AE should be assigned, the AE will be assigned to all relevant treatment periods or settings.

A listing of non-treatment emergent AEs occurring before start of study treatment will be provided (with a flag to identify those AEs that continued into on-study treatment cycles). All other listings of AEs will include all AEs with onset on or after the first study drug treatment (including AEs starting more than 28 days after the last administration of study treatment).

AEs associated with COVID-19 will be listed. Confirmed or suspected COVID-19 AEs, as well as AEs associated with COVID-19 will be summarized separately for each study phase.

4.5.3 Additional Safety Assessments

Additional safety assessments will be summarized separately for each study phase. For the neoadjuvant phase, summaries will be produced by study treatment and chemotherapy option, and overall. For the PH FDC SC cohort in the adjuvant phase, summaries will be produced by period and treatment setting, and overall. For the cross-over period, summaries will be produced by treatment setting sequence, and overall.

4.5.3.1 Laboratory Data

Relevant laboratory data will be summarized over time. Appropriate laboratory data will be graded according to NCI CTCAE v5.0 and will be summarized descriptively. Additionally, shift tables of gradable laboratory tests will be produced to summarize the baseline and maximum post-baseline severity grade.

Potential Hy's law patients will be listed based on the laboratory data if either of the following is met:

- Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 × ULN
- Treatment-emergent ALT or AST $>$ 3$\times$ baseline value in combination with clinical jaundice

4.5.3.2 Vital Signs and ECOG Performance Status

Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) and changes in vital signs will be summarized by visit.

The ECOG performance status will be summarized via the number and percentage of participants for each combination of baseline and worst post-baseline ECOG scores.

4.5.3.3 ECGs

Electrocardiogram (ECG) data and changes in ECGs will be summarized by visit.

4.5.3.4 LVEF

LVEF data and changes in LVEF will be summarized by visit.

4.5.3.5 Use of Anaphylactic Medications

The number of patients who received anaphylactic medications during the adjuvant phase will be summarized and the type of medications received will be detailed.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

Enrollment, patient disposition, patients who switched from P+H IV (arm A) to PH FDC SC (arm B), patients from arm E who switched from Trastuzumab Emtansine to PH FDC SC and discontinuation from the study will be summarized separately for each study phase/period. The reasons for study phase/period discontinuation or study discontinuation will also be tabulated. Major protocol deviations will be summarized by treatment as defined below.

For the neoadjuvant phase, summaries will be produced on the FASab by study treatment and overall. For the PH FDC SC cohort in the adjuvant phase, summaries will be produced on the FAScd+ by treatment setting sequence and overall. For the trastuzumab emtansine IV arm in the adjuvant phase, summaries will be produced on the SASe. For the cross-over period, summaries will be produced on the mITTcross by treatment setting sequence and overall.

4.6.2 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 separately for each study phase.

For the neoadjuvant phase, summaries will be produced on the SASab by study treatment and overall. For the PH FDC SC cohort in the adjuvant phase, summaries will be produced on the FAScd+ by treatment setting sequence and overall. For the trastuzumab emtansine IV arm in the adjuvant phase, summaries will be produced on the SASe. For the cross-over period, summaries will be produced on the mITTcross by treatment setting sequence and overall.

4.6.3 Diagnosis of Breast Cancer Recurrence or Second Primary Cancer

A listing of tumor response assessments will be provided on the following analysis sets: SASab, SAScd+ and SASe.

4.6.4 Pregnancy

A listing of pregnancy tests will be provided on the SASab.

4.7 INTERIM ANALYSES

No interim analyses are planned.

5. REFERENCES

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