Official Title: A Randomized, Multicenter, Open-Label Cross-Over Study to Evaluate Patient Preference and Satisfaction of Subcutaneous Administration of the Fixed-Dose Combination of Pertuzumab and Trastuzumab in Patients With HER2-Positive Early Breast Cancer

NCT Number: NCT03674112

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STATISTICAL ANALYSIS PLAN

TITLE: **A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PATIENT PREFERENCE AND SATISFACTION OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**

PROTOCOL NUMBER: MO40628

STUDY DRUG: Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration (RO7198574)

VERSION NUMBER: 1.1

IND NUMBER: 131009

EUDRACT NUMBER: 2018-002153-30

SPONSOR: F. Hoffmann-La Roche Ltd

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[redacted], F. Hoffmann-La Roche Ltd

DATE FINAL: 05-Sep-2019

DATE(S) AMENDED See electronic date stamp below.

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
07-Apr-2020 16:21:25	Company Signatory	[redacted]

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan (SAP) for Study MO40628 (PHranceSCa) has been amended to incorporate the following changes.

VERSION 1.1:

- Removing the logistic regression in section 4.5.1 to model patient preference according to treatment sequence and stratification factors. This was not mandated by the protocol and would not provide stable results in this small trial.
- Clarification of the subgroups to be analyzed (sections 4.5.1 and 4.5.5)
- Aligning the definition of Hy's law to the current version of the protocol in section 4.7.3

Additional minor changes have been made to improve clarity and consistency.

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LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse events
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CSR	clinical study report
DDFS	distant disease-free survival
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organization for the Research and Treatment of Cancer
FDA	Food and Drug Administration
FDC SC	Fixed-dosed combination formulation for subcutaneous administration
HCP	healthcare professional
HER2	human epidermal growth factor receptor 2
HER2+	HER2-positive
Herceptin IV	Herceptin for IV administration
Herceptin SC	Herceptin for SC administration
HRQoL	health-related quality of life
ICH	International Conference on Harmonization
IDFS	invasive disease-free survival
ITT	Intent-to-treat
IV	intravenous(ly)
IxRS	Interactive voice/web response system
KM	Kaplan Meier
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
pCR	pathologic complete response
PgR	progesterone receptor
PFS	progression free survival

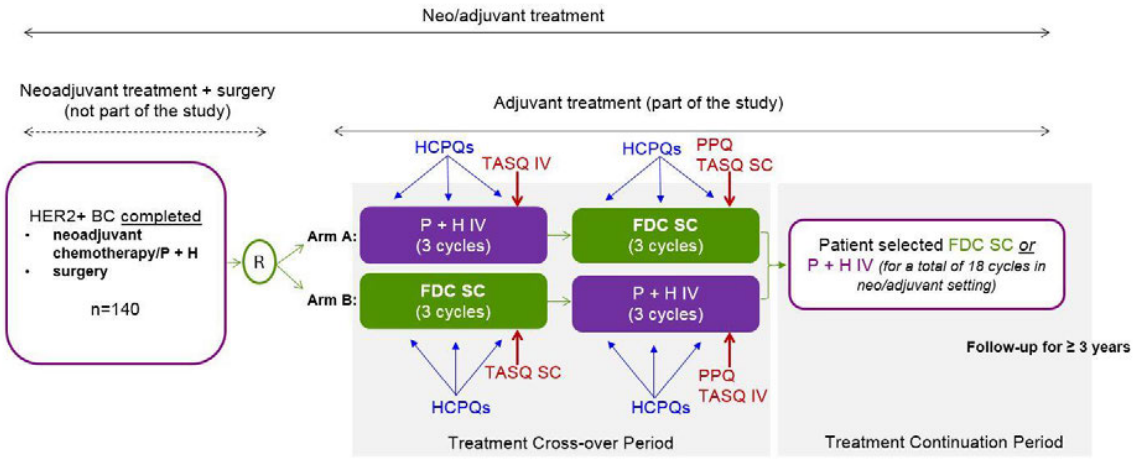
Abbreviation	Definition
PPQ	Patient Preference Questionnaire
PRO	patient reported outcome
PS	performance status
PT	preferred term
QoL	quality of life
SAF	safety population
SAP	statistical analysis plan
SC	subcutaneous(ly)
SOC	System Organ Class
TASQ-IV	Therapy Administration Satisfaction Questionnaire – intravenous
TASQ-SC	Therapy Administration Satisfaction Questionnaire – subcutaneous
ULN	upper limit of normal range

1. BACKGROUND

This Statistical Analysis Plan (SAP) describes the analyses that are planned to be performed for the Clinical Study Reports (CSRs) of Study MO40628 (PHranceSCa).

2. STUDY DESIGN

This is a Phase II, randomized, multi-centre, multinational, open-label, cross-over study in adult patients who have completed neoadjuvant chemotherapy with neoadjuvant Perjeta and Herceptin and have undergone surgical treatment of HER2+ EBC. The primary objective for this study is to evaluate patient preference for pertuzumab and trastuzumab FDC SC. An overview of the study design is provided in the figure below.



Abbreviations: IV: intravenous; P+H: Perjeta + Herceptin; FDC SC: subcutaneously administered fixed-dose combination of pertuzumab and trastuzumab; HCPQs: Healthcare Professional Questionnaires; PPQ: Patient Preference Questionnaire; SC subcutaneous; TASQ: Therapy Administration Satisfaction Questionnaire

Patients will be randomized following surgery and the completion of (neo)adjuvant chemotherapy in a 1:1 ratio to treatment Arm A (P+H IV followed by pertuzumab and trastuzumab FDC SC) or treatment Arm B (pertuzumab and trastuzumab FDC SC followed by P+H IV).

Patients randomized to Arm A will receive P+H IV (3 cycles) followed by pertuzumab and trastuzumab FDC SC (3 cycles). Patients randomized to Arm B will receive pertuzumab and trastuzumab FDC SC (3 cycles) followed by P+H IV (3 cycles). This period of 3+3 cycles in both treatment arms constitutes the study Treatment Cross-over Period.

The 6 study treatment cycles of pertuzumab and trastuzumab FDC SC and P+H IV received during the Treatment Cross-over Period and Perjeta and Herceptin treatment cycles received in the neoadjuvant setting prior to study entry will be considered part of

the total 18 anti-HER2 treatment cycles planned for all study patients. Following completion of the Treatment Cross-over Period, patients will enter the Treatment Continuation Period wherein they will receive the remaining anti-HER2 treatment cycles required to complete their 18 planned cycles unless disease recurrence, unacceptable toxicity or patient withdrawal from treatment necessitates early treatment cessation. Study treatment during this period will be either P+H IV or pertuzumab and trastuzumab FDC SC as selected by the patient at the end of the Treatment Cross-over Period.

Patients who, by the investigator's assessment, cannot tolerate pertuzumab and trastuzumab FDC SC or P+H IV may be allowed to receive P+H IV or pertuzumab and trastuzumab FDC SC, respectively, for their remaining planned anti-HER2 treatment cycles.

The main analysis of the primary endpoint will take place after all patients have received 3 cycles of pertuzumab and trastuzumab SC and 3 cycles of P+H IV and have completed the Patient Preference Questionnaire.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The primary endpoint is the proportion of patients indicating an overall preference for pertuzumab and trastuzumab FDC SC in Question 1 of the Patient Preference Questionnaire (PPQ). Question 1 of the PPQ is as follows: "All things considered, which method of administration did you prefer?"

2.2.2 Secondary Endpoints

Secondary endpoints linked to secondary objectives are:

- Patient responses to Question 1 of the TASQ-SC and TASQ-IV: "How satisfied or dissatisfied were you with the SC injection?" and respectively "with the IV infusion?"
- Proportion of patients who select pertuzumab and trastuzumab FDC SC for the study Treatment Continuation Period
- HCP responses to the HCP Questionnaires, by summarizing responses to individual questions
- Change in treatment-related symptoms and function from baseline and over time as assessed by mean and mean change from baseline scores, as assessed by the EORTC QLQ-C30
- Mean and mean changes from baseline score in HRQoL by cycle as assessed by the Global Health Status/HRQoL scale (items 29 and 30) of the EORTC QLQ-C30

2.2.2.1 Secondary Safety Endpoints

The first secondary safety objective is to evaluate the safety and tolerability of pertuzumab and trastuzumab FDC SC and P+H IV during the study Treatment Cross-over Period and the entire adjuvant treatment period (Treatment Crossover Period + Treatment Continuation Period) based on the following endpoints:

- Incidence, nature and severity of all AEs (adverse events), ≥ Grade 3 AEs, serious adverse events (SAEs) and cardiac AEs (including left ventricular ejection fraction [LVEF] events)
- Incidence of premature withdrawal from study treatment
- Targeted vital signs and physical findings
- Targeted clinical laboratory test results

The second safety objective is to evaluate the safety of switching from pertuzumab and trastuzumab FDC SC to P+H IV and from P+H IV to pertuzumab and trastuzumab FDC SC based on:

- Incidence, nature and severity of all AEs, ≥ Grade 3 AEs, SAEs and cardiac AEs (including LVEF events) during the study Treatment Cross-over Period by treatment sequence and actual treatment.

For all safety endpoints, AE severity will be determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0)

2.2.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints linked to secondary efficacy objectives are:

- Invasive Disease-Free Survival (IDFS), defined as the time from randomization to the first occurrence of one of the following events:
  - Ipsilateral invasive breast tumour recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)
  - Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast)
  - Distant recurrence (i.e., evidence of breast cancer in any anatomic site other than the two above mentioned sites that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer)
  - Contralateral invasive breast cancer
  - Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified, if possible)

  Note: Ipsilateral or contralateral *in situ* disease and second primary non-breast cancers (including *in situ* carcinomas and non-melanoma skin cancers) will not be counted as recurrence.

- Invasive disease-free survival including second primary non-breast cancer, defined as IDFS with second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and *in situ* carcinoma of any site) included as an event
- Distant Disease-Free Survival (DDFS) is defined as the time from randomization to the date of distant breast cancer recurrence.
- Overall Survival (OS) is defined as the time from randomization to death from any cause.

2.3 DETERMINATION OF SAMPLE SIZE

The primary study objective is to estimate the proportion of patients who express a preference for pertuzumab and trastuzumab FDC SC.

The planned total sample size of 140 patients is based on an assumed rate of 70% of patients preferring pertuzumab and trastuzumab FDC SC. To achieve a distance of approximately ± 8% from the estimated proportion to 95% CI limits, a total of 126 patients are needed for the evaluation of preference. The final target sample size was increased to approximately 140 patients to allow for 10% of the patients not providing an evaluable preference assessment.

There will be no formal hypothesis test for the primary endpoint.

2.4 ANALYSIS TIMING

The primary study analysis will take place when all study patients have completed their last study treatment administration in the Treatment Cross-over Period. Summaries of secondary study endpoints, including patient reported TASQ and EORTC QLQ-C30 responses, selection of treatment administration method for the Treatment Continuation Period, HCP reported HCPQ responses and safety endpoints will be included in the primary analysis.

An interim analysis will be conducted to support a planned regulatory filing for FDC, which will consist of a subset of the analyses planned for the primary analysis. (see Section 4.9). The results of this interim analysis will be evaluated by a Sponsor's Internal Monitoring Committee.

The final study analysis that includes all secondary safety and efficacy endpoints will be conducted after the end of the study.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Randomization to Arm A (P+H IV followed by pertuzumab and trastuzumab FDC SC) or Arm B (pertuzumab and trastuzumab FDC SC followed by P+H IV) will occur via a web-based response system (IWRS) in a 1:1 ratio.

Randomization will be stratified according to:

- Neoadjuvant chemotherapy regimen (anthracyclines + taxanes vs. carboplatin + taxanes vs. taxanes only),
- Neoadjuvant treatment response (pCR vs. non-pCR),
- Hormone receptor status (positive [ER-positive and/or PgR-positive] vs. negative [ER-negative and PgR-negative]).

3.2 INDEPENDENT REVIEW FACILITY

Not applicable

3.3 DATA MONITORING

An interim analysis will be conducted to support a planned regulatory filing for FDC, which will consist of a subset of the analyses planned for the primary analysis. The results of this interim analysis will be evaluated by a Sponsor's Internal Monitoring Committee.

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 patients in this study. The IMC will be responsible for monitoring the safety of patients in the study and will make recommendations to the Therapeutic Area Head 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 will be detailed in the IMC charter.

4. STATISTICAL METHODS

The analyses outlined in this SAP supersede those specified in the protocol for the purpose of a regulatory filing.

4.1 ANALYSIS POPULATIONS

The analysis populations are defined as follows:

- Intent-To-Treat (ITT) Population: All randomized patients, allocated to their randomized treatment arm, whether or not the assigned study treatment was received.
- Modified ITT (mITT) Population: All randomized patients, allocated to their randomized treatment arm, who received at least one dose by both SC and IV routes of administration during the Treatment Cross-over Period and subsequently answered at least Question 1 of the PPQ.
- Patient reported outcome (PRO) evaluable Population for analysis of the EORTC QLQ-C30: The PRO-evaluable population includes all patients in the ITT population with a baseline EORTC QLQ-C30 assessment and at least one post-baseline EORTC QLQ-C30 assessment.

- Safety Population: All patients who received at least one dose of any study drug categorized according to the study drug administered.

For all efficacy analyses, patients will be grouped according to the treatment sequence assigned at randomization, unless otherwise specified.

For all safety analyses, patients will be grouped according to the treatment actually received, unless otherwise specified.

4.2 TREATMENT PERIODS

In this study, there are 2 main treatment periods:

- The Treatment Cross-over Period will consist of maximum 6 study treatment cycles of pertuzumab and trastuzumab FDC SC (maximum 3 cycles) and P+H IV (maximum 3 cycles). The cross-over period starts immediately after completion of the neoadjuvant treatment.
- The Treatment Continuation Period: Following completion of the Treatment Cross-over Period, patients will enter the Treatment Continuation Period wherein they will receive the remaining anti-HER2 treatment cycles required to complete their 18 planned cycles unless disease recurrence, unacceptable toxicity or patient withdrawal from treatment necessitates early treatment cessation. Study treatment during this period will be either P+H IV or pertuzumab and trastuzumab FDC SC as selected by the patient at the end of the Treatment Cross-over Period.

4.3 ANALYSIS OF STUDY CONDUCT

Enrolment, eligibility violations and patient disposition will be summarized by treatment sequence and overall in the ITT and mITT populations. Reasons for patient's study treatment discontinuation and patient's reasons for study discontinuation will be listed by patient and summarized in ITT population by treatment sequence and overall. Major protocol deviations will be listed and summarized in the ITT and mITT populations by treatment sequence and overall and evaluated for their potential effects on the interpretation of study results.

Median follow-up on study, estimated with corresponding 95% CI by the reverse Kaplan-Meier approach, will be presented.

Follow-up time is calculated from the date of the Cycle 1 visit. Patients who died on study are censored at the time of death. Other patients are considered to have been followed until the date of study completion or discontinuation. If neither of those dates is available, the date of the last recorded visit will be used.

4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, weight, stratification variables and other relevant baseline characteristics will be summarized using means, standard deviations (SDs), medians, ranges and inter-quartile ranges for continuous variables and

frequencies and percentages for categorical variables, as appropriate. Summaries will be presented overall and by treatment sequence in ITT population.

Previous and concurrent medical history will be summarized overall and by treatment sequence in ITT population.

Prior and follow-up anti-cancer therapy or surgery, tumor characteristics and pCR results at screening will be summarized overall and by treatment sequence in ITT population.

4.5 ANALYSIS

4.5.1 Primary Endpoint

The primary objective of this study is to evaluate patient preference for pertuzumab and trastuzumab FDC SC based on the proportion of patients indicating an overall preference for pertuzumab and trastuzumab FDC SC in Question 1 of the PPQ. Question 1 of the PPQ is as follows: “All things considered, which method of administration did you prefer?”.

Patient preference will be summarized by treatment sequence and overall and presented in tables based on the mITT population. In order to assess the robustness of the primary analysis the analysis of the primary endpoint will be repeated for the ITT population as a sensitivity analysis.

The primary analysis of the primary endpoint will take place once the last patient has completed the last study treatment administration in the Treatment Cross-over Period.

Patient preference will be summarized by presenting the number and percentage of patients in each category (SC, IV and No preference). A point estimate with associated exact Clopper-Pearson binomial 95% CI for the proportion of patients who preferred pertuzumab and trastuzumab FDC SC will be calculated for the mITT and the ITT populations and will be described by treatment sequence and overall.

Patient preference will also be summarized by presenting the number and percentage of patients in each category (SC, IV and No preference) by stratification factors: neoadjuvant chemotherapy regimen (anthracyclines + taxanes / carboplatin + taxanes / taxanes only), neoadjuvant treatment response (pCR / non-pCR) and hormone receptor status (positive / negative).

Exploratory subgroup analyses will be performed for the mITT population by:

- Age (<65 years vs. ≥65 years and <75 years vs. ≥ 75 years)
- Race (White, Black, Asian, Other)
- Body Weight (categories defined by weight percentiles)
- Neoadjuvant treatment response (pCR vs. non-pCR)

- Number of neoadjuvant Perjeta and Herceptin cycles (< 4 cycles vs. ⩾4 cycles)

4.5.2 Secondary Endpoints

4.5.2.1 Patient Responses to Questions 2 and 3 of the PPQ

For patients who reported a preference for one of the two administration routes 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 (IV and SC) on the mITT and the ITT populations by treatment sequence and overall.

4.5.2.2 Patient Responses to Questions of the TASQ-SC and TASQ-IV

The TASQ is a 12-item questionnaire measuring the impact of the mode of treatment administration on five domains: Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction. The Physical Impact domain comprises of 3 items (Q2: Pain experience, Q3: Swelling experience, Q4: Redness experience), the Psychological Impact domain contains one item (Q5: Feeling restricted by SC injection/IV infusion), The Impact on Activities of Daily Living contains one item (Q8: Lost/gained time), The Convenience domain contains 2 items (Q6: Is it convenient to get SC injection/IV infusion, Q7: Bothered by the amount of time to get SC injection/IV infusion), and the Satisfaction domain includes 2 items (Q1: How satisfied or dissatisfied are you with the SC injection/IV infusion, Q12: Would you recommend the way you received the treatment). All 9 TASQ items included in the above domains have five response options:

- Reverse-coded response values will be created for eight of the TASQ items (Q1, Q2, Q3, Q4, Q5, Q6, Q7 and Q12)

In addition, there are three questions in the TASQ (Q9, Q10, Q11) that are not part of the above domains. These three questions will be analyzed separately and presented descriptively.

Patient assessed satisfaction with pertuzumab and trastuzumab FDC SC and P+H IV will be based on patient responses to Question 1 of the TASQ-SC and TASQ-IV respectively.

The patient satisfaction will be described by treatment sequence and overall in two ways: first as a categorical variable with the number and proportion of patient responses to each modality of the question (very satisfied, satisfied, …, very dissatisfied), and secondly as a continuous variable with descriptive statistics.

In addition, the patient responses of the TASQ-SC and TASQ-IV will be summarized by domain (physical impact, psychological impact, impact on activities of daily living, convenience and satisfaction).

For the three domains that contain more than one item (Physical Impact, Convenience and Satisfaction), the algorithm will be the following:

If there are no missing responses, the domain will be scored using the formula:

Domain score = [(Sum of completed item responses / Number of completed items) - 1] x 100 / (Maximum possible item response value – Minimum possible item response value)

However, if there are any missing responses within a domain then the domain will not be scored (i.e. a missing value is assigned to the domain).

Since the maximum possible item response value is 5 and the minimum possible response value is 1 for all TASQ items, a simpler way to represent the above formula for the TASQ domains is:

TASQ domain score = (Mean of completed item responses – 1) x 25

Descriptive statistics will be computed for these three domains by treatment sequence and overall. Descriptive p-values, not adjusted for multiple testing, might be calculated to assess differences between groups, at timepoints and/or by treatment sequence.

The two domains that contain only one item (Psychological Impact and Impact on Activities of Daily Living) will be described by treatment sequence and overall in the same way as the patient satisfaction in Question 1: first as a categorical variable with the number and proportion of patient responses to each modality of the question, and secondly as a continuous variable with descriptive statistics.

The three descriptive questions (Q9, Q10, Q11) that are not part of the above domains will be summarized individually by the number and proportion of patient responses to each modality of the question.

All TASQ analyses will be performed on the mITT population.

4.5.2.3 Patient's Choice of Treatment for the Treatment Continuation Period

The proportion (and 95%CI) of patients who select each treatment administration route for the Treatment Continuation Period will be summarized on the ITT Population. Results will be displayed by treatment sequence and overall.

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

4.5.2.4 Healthcare Professional Questionnaire (HCPQ)

Healthcare professional perception of time/resource use and convenience with pertuzumab and trastuzumab FDC SC will be assessed by summarizing responses to individual questions of the HCPQs on the ITT population by treatment sequence and overall.

Healthcare Professional Questionnaire-Treatment Room

The number of HCPQs completed, the specialities of Healthcare Professional Respondents (Nurse, Pharmacy Technician, Oncologist, Gynaecologist), the number of countries and number of patients by country will be summarized overall.

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

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

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

Missing data will be reported by timepoint.

Impact on Clinical Management and Clinical Efficiency

Responses to individual questions 2 to 8 will be summarized overall, by healthcare professional speciality and by individual country.

Healthcare Professional Questionnaire-Drug Preparation Room

The number of HCPQs completed, the specialities of Healthcare Professional Respondents (Nurse, Pharmacist, Pharmacy Technician), the number of countries and number of patients by country will be summarized overall.

Experience with 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 speciality 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 speciality and by individual country.

4.5.2.5 EORTC QLQ-C30

EORTC data will be analyzed based on the PRO-evaluable population, unless specified otherwise.

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. PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm on the ITT population.

4.5.3 Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed on the ITT population.

4.5.3.1 Invasive Disease-Free Survival

- Invasive disease-free survival is defined as the time from randomization to the first occurrence of one of the following events:
  - Ipsilateral invasive breast tumour recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)
  - Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast)
  - Distant recurrence (i.e., evidence of breast cancer in any anatomic site other than the two above mentioned sites that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer)
  - Contralateral invasive breast cancer
  - Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified, if possible)

  Note: Ipsilateral or contralateral *in situ* disease and second primary non-breast cancers (including *in situ* carcinomas and non-melanoma skin cancers) will not be counted as recurrence.

Patients who have not experienced invasive disease at the time of analysis will be censored i) at the time of the last clinical breast examination if post-baseline clinical breast examination ii) on the date of randomization + 1 day if no post-baseline clinical breast examination.

Kaplan-Meier methodology will be used to estimate median IDFS for each treatment sequence and overall and to construct survival curves. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median IDFS for each treatment sequence (Brookmeyer and Crowley 1982).

In addition, the 12-month, 24-month and 36-month IDFS rates and 95% CI will be provided in each treatment sequence and overall.

Comparable IDFS rates will be explored by neoadjuvant chemotherapy regimen (anthracyclines + taxanes / carboplatin + taxanes / taxanes only), neoadjuvant treatment response (pCR / non-pCR), hormone receptor status (positive / negative), node status at diagnosis (positive / negative), and number of neoadjuvant PH cycles (<4 / >=4).

4.5.3.2 Invasive Disease-Free Survival Including Second Primary Non-Breast Cancer (IDFS2)

Invasive disease-free survival including second primary non-breast cancer (IDFS2) is defined as IDFS with second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and *in situ* carcinoma of any site) included as an event.

IDFS2 will be analyzed in a similar manner as IDFS.

4.5.3.3 Distant Disease-Free Survival (DDFS)

Distant disease-free survival (DDFS) is defined as the time from randomization to the date of distant breast cancer recurrence.

DDFS will be analyzed in a similar manner as IDFS.

4.5.3.4 Overall Survival (OS)

Overall survival is defined as the time from randomization to death due to any cause. Patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization+ 1 day.

OS will be analyzed in a similar manner as IDFS.

4.5.4 Sensitivity Analyses

The analyses defined in Section 4.5.1 will serve as the sensitivity analyses.

In addition, if an unexpected sequencing effect will be observed, more exploratory post-hoc analyses might be performed.

4.5.5 Subgroup Analyses

The following subgroups will be considered:

- Age (<65 years vs. ≥65 years and <75 years vs. ≥75 years)

- Race (White, Black, Asian, Other)
- Body Weight (categories defined by weight percentiles)
- Neoadjuvant chemotherapy regimen (anthracyclines + taxanes, carboplatin + taxanes, taxanes only)
- Neoadjuvant treatment response (pCR, non-pCR),
- Hormone receptor status (positive [ER-positive and/or PgR-positive], negative [ER-negative and PgR-negative])
- Clinical stage at presentation (II-IIIA; IIIB-IIIC)
- Number of prior neoadjuvant PH cycles (<4 vs. ≥4)
- Node status at diagnosis (positive, negative)
- Tumor diameter (<2 cm vs. ≥2 cm – <5 cm vs. ≥5 cm)

4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable

4.7 SAFETY ANALYSES

All safety analyses will be performed on the safety population, unless specified otherwise.

4.7.1 Exposure of Study Medication

Exposure to study drug will be summarized by treatment (Cross-Over Period IV, Cross-Over Period SC, Continuation Period IV, Continuation Period SC) and by treatment sequence (IV/FDC SC, FDC SC/IV). The total number of cycles initiated will be summarized both by descriptive statistics and by presenting the number and percentage of patients in each category. The number and percentage of patients who have initiated their 6th cycle will also be summarized. A patient will be considered as having initiated a cycle if at least one (non-null) dose of any study drug has been administered in the corresponding cycle.

Study drug administration details will be summarized by descriptive statistics and will include percentage of missed doses, percentage of cycles delayed, average number of days delayed and percentage of cycles interrupted. Study drug administration details will be summarized by treatment and treatment sequence.

4.7.2 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 4.0 (NCI CTCAE v4.0). 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.

Incidence of AEs will be presented by treatment period (FDC SC Cross-Over Period, IV Cross-Over Period, FDC SC Continuation Period, IV Continuation Period) and overall. In addition, selected tables will be presented by treatment sequence (FDC SC/IV, IV/FDC SC) and for the overall cross-over for AEs starting during the cross-over period only.

Only adverse events occurring on or after the first dose of any study treatment in the Cross-Over period will be included in the summary tables. Adverse events occurring prior the first dose of any study treatment in the Cross-Over period will be summarized separately as 'baseline signs and symptoms'.

An AE will be assigned to a route of administration if it occurred on or after the first dose by that route and prior to the first (subsequent) date of a treatment by another other route. If there is no subsequent treatment by the other route then the 28 day cut off will be applied. For a patient completing the 6 cycles of the crossover treatment and continuing treatment, the AEs to be included for the crossover period are those up until the first dose of continuation medication. AEs during the first 3 cycles of treatment are selected if they started during the first 3 cycles of the treatment assigned to period 1. If a patient changed treatment before completing all 3 cycles of the period 1 treatment then only the AEs starting during the relevant cycles will be selected. If there is no subsequent treatment by the other route 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 the AE should be assigned, the AE will be assigned to all relevant treatment periods.

Adverse events will be summarized by presenting the number and percentage of patients having any event, events leading to discontinuation or interruption of study drug, cardiac events, and events by CTC grade, relationship and outcome.

This summary will be presented for:

- Adverse events
- Adverse events during the cross-over period by treatment sequence
- Adverse events during the first 3 cycles of treatment versus cycles 4-6
- Serious adverse events
- Serious adverse events by Age
- Serious adverse events during the cross-over period by treatment sequence
- Serious adverse events during the first 3 cycles of treatment versus cycles 4-6

AEs by body weight (categories defined by weight percentiles) will be summarized by presenting the number and percentage of patients and number of events for:

- Adverse events by Body Weight

- Adverse events by Body Weight during the first 3 cycles of treatment versus cycles 4-6
- Serious adverse events by Body Weight
- Serious adverse events by Body Weight during the first 3 cycles of treatment versus cycles 4-6

Summary tables by system organ class (SOC) and preferred term of the number and percentage of patients having events will be presented for:

- Adverse events
- Adverse events during the cross-over period by treatment sequence
- Serious adverse events
- Serious adverse events during the cross-over period by treatment sequence
- Serious adverse events by highest NCI CTCAE grade
- Serious adverse events by Body Weight
- Adverse events Grade 3 or more
- Adverse events Grade 3 or more during the cross-over period by treatment sequence
- Related adverse events
- Related adverse events during the cross-over period by treatment sequence
- Related serious adverse events
- Related serious adverse events during the cross-over period by treatment sequence
- Adverse events leading to study drug discontinuation
- Adverse events leading to study drug discontinuation during the cross-over period by treatment sequence
- Adverse events leading to study drug interruption
- Adverse events leading to study drug interruption during the cross-over period by treatment sequence
- Adverse events resulting in death
- Cardiac AEs (including LVEF events)
- Cardiac AEs (including LVEF events) during the cross-over period by treatment sequence
- Adverse events of special interest (see Section 5.2.3 in the protocol)
- Adverse events of special interest by highest NCI CTCAE grade
- Serious adverse events of special interest
- Serious adverse events of special interest by highest NCI CTCAE grade
- Infusion-related reactions (Systemic)
- Infusion-related reactions (Systemic) during the cross-over period by treatment sequence

- Injection-related reactions (Systemic)
- Injection-related reactions (Systemic) during the cross-over period by treatment sequence
- Injection-Site reactions (Local)
- Injection-Site reactions (Local) during the cross-over period by treatment sequence

To evaluate the safety of switching from pertuzumab and trastuzumab FDC SC to P+H IV and from P+H IV to pertuzumab and trastuzumab FDC SC, the following summary tables by system organ class and preferred term will be presented for the Treatment Cross-over Period by treatment sequence and actual treatment:

- Adverse events during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm
- Serious adverse events during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm
- Adverse events Grade 3 or more during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm
- Related adverse events during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm
- Related serious adverse events during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm
- Adverse events leading to study drug discontinuation during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm
- Adverse events leading to study drug interruption during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm
- Cardiac AEs (including LVEF events) during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm
- Infusion-related reactions (Systemic) during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm
- Injection-related reactions (Systemic) during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm
- Injection-Site reactions (Local) during the first 3 cycles of treatment versus cycles 4-6 by actual treatment arm

In addition, the following summary tables will be provided by preferred term:

- Most frequent adverse events by preferred term (>=5% events in any group)
- Most frequent adverse events during the cross-over period by treatment sequence and preferred term (>=5% events in any group)
- Most frequent adverse events during the first 3 cycles of treatment versus cycles 4-6 by preferred term (>=5% events in any group)

A listing of Non-treatment emergent AEs (i.e. those occurring before start of study treatment) will be provided. All listings of AEs will include all AEs with onset on or after the first study drug treatment up to the data cutoff date.

All deaths and causes of deaths will be summarized by treatment arm and overall.

4.7.3 Laboratory Data

Laboratory data will be summarized descriptively over time including change from baseline by treatment sequence and overall.

Laboratory data will be classified according to NCI CTCAE 4.0. Highest NCI CTCAE grade post-baseline will also be reported and shift tables from baseline to worst post-baseline will be presented by treatment sequence.

Potential Hy's law patients will be listed. Potential Hy's law cases are defined as either of the following:

- Treatment-emergent ALT or AST >3xbaseline value (in earlier studies 3xULN) in combination with total bilirubin >2xULN (of which $\geqslant$35% is direct bilirubin)

- Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice.

4.7.4 Vital Signs and ECOG Performance Status

Vital signs parameters include:

- Temperature (°C)
- Systolic blood pressure (SBP seated position) (mmHg)
- Diastolic blood pressure (DBP seated position) (mmHg)
- Weight (kg)
- Heart rate (beats/min)
- Respiratory rate (breaths/min)

Vital signs and ECOG performance status will be summarized by treatment sequence over time and overall. Shift table from baseline versus worst post-baseline will be presented by treatment sequence and overall.

All vital signs data including change from baseline will be listed.

4.7.5 Electrocardiograms

The baseline ECG of the patients and results of on-study ECGs will be summarized by treatment sequence and overall.

4.8 MISSING DATA

For the calculation of time to onset missing day will be replaced with the 1st of the month, missing month will be replaced with January. Other missing, unused and spurious data will be dealt with as such. There is no intention to implement any procedure for replacing any other missing data.

4.9 INTERIM ANALYSES

An interim analysis, which will consist of a subset of the analyses planned for the primary analysis, will be conducted to support a planned regulatory filing for FDC. The results of this interim analysis will be evaluated by the Sponsor's Internal Monitoring Committee.

For this interim analysis a cut-off date will be implemented after the first approximately 50 patients will have completed the cross-over phase. Assuming a drop-out rate of 10% after 50 patients accrued there would be 45 evaluable patients. With this sample size, the estimation precision (95%CI) for an observed SC preference rate of 75% would be 60% to 87% and for an observed rate of 85% it would be 70% to 94%.

The subset of analyses will consist of: demographics, disposition, PPQ, TASQ SC/IV and safety.

5. REFERENCES

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Appendix 1
Protocol Synopsis

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PATIENT PREFERENCE AND SATISFACTION OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**
PROTOCOL NUMBER:	MO40628
VERSION NUMBER:	2
EUDRACT NUMBER:	2018-002153-30
IND NUMBER:	131009
TEST PRODUCT:	Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration (RO7198574)
PHASE:	II
INDICATION:	HER2-positive Early Breast Cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate patient reported preference for a subcutaneously administered fixed-dose combination formulation (FDC SC) of pertuzumab and trastuzumab compared with intravenously (IV) administered Perjeta® and Herceptin® formulations (P+H IV) in patients with HER2-positive (HER2+) early breast cancer (EBC). The study will also evaluate patient reported satisfaction with pertuzumab and trastuzumab FDC SC and health-related quality of life (HRQoL) outcomes; Healthcare professionals (HCPs) perception of time/resource use and convenience of pertuzumab and trastuzumab FDC SC and P+H IV; as well as the safety and efficacy of each study regimen.

Specific objectives and corresponding endpoints for the study are outlined in the following table.

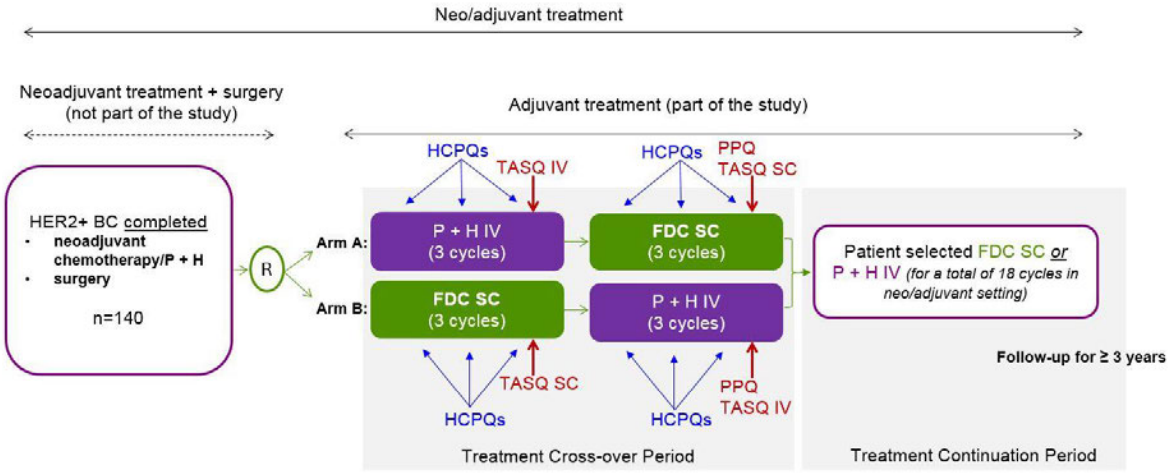
Table of Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate patient preference for pertuzumab and trastuzumab FDC SC	• Proportion of patients who preferred pertuzumab and trastuzumab FDC SC with treatment preference assessed via Question 1 of the PPQ

Secondary Objectives	Corresponding Endpoints
• To evaluate patient assessed satisfaction with route of administration of pertuzumab and trastuzumab FDC SC and route of administration of P+H IV	• Patient responses to Question 1 of the TASQ-SC and TASQ-IV
• To evaluate patients' choice of pertuzumab and trastuzumab FDC SC for the Treatment Continuation Period	• Proportion of patients who select pertuzumab and trastuzumab FDC SC for the study Treatment Continuation Period
• To evaluate HCP perception of time/resource use and convenience with pertuzumab and trastuzumab FDC SC	• HCP responses to the HCPQs, by individual question
• To evaluate HRQoL with pertuzumab and trastuzumab FDC SC and P+H IV	• Change in symptoms and function from baseline and over time as assessed by EORTC QLQ-C30 scores • Mean and mean changes from baseline score in HRQoL by cycle as assessed by the Global Health Status / overall QoL scale (items 29 and 30) of the EORTC QLQ-C30.
Secondary Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of pertuzumab and trastuzumab FDC SC and P+H IV during the study Treatment Cross-over Period and the entire adjuvant treatment period (Treatment Cross-over Period + Treatment Continuation 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 v4.0 • Incidence of premature withdrawal from study treatment • Targeted vital signs and physical findings • Targeted clinical laboratory test results
• To evaluate the safety of switching from pertuzumab and trastuzumab FDC SC to P+H IV and from P+H IV to pertuzumab and trastuzumab FDC SC	• Incidence, nature and severity of all AEs, ≥ Grade 3 AEs, SAEs and cardiac AEs (including LVEF events) with severity determined according to NCI CTCAE v4.0 during the study Treatment Cross-over Period by treatment arm

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the long-term efficacy of the pertuzumab and trastuzumab FDC SC and P+H IV	• IDFS, defined as the time from randomization to the first occurrence of one of the following events: o Ipsilateral invasive breast tumour recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion) o Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast) o Distant recurrence (i.e., evidence of breast cancer in any anatomic site other than the two above mentioned sites that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer) o Contralateral invasive breast cancer o Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified, if possible) Note: Ipsilateral or contralateral *in situ* disease and second primary non-breast cancers (including *in situ* carcinomas and non-melanoma skin cancers) will not be counted as recurrence. • IDFS including second primary non-breast cancer, defined as IDFS with second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and *in situ* carcinoma of any site) included as an event • DDFS, defined as the time from randomization to the date of distant breast cancer recurrence • OS, defined as the time from randomization to death from any cause.

AE: adverse event; DDFS: distant disease-free survival; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; HCP: healthcare professional; HCPQ: Healthcare Professional Questionnaire; HRQoL: health-related quality of life; IDFS: invasive disease-free survival; LVEF: left ventricular ejection fraction; NCI CTCAE v4.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; OS: overall survival; P+H IV: intravenously administered Perjeta and Herceptin formulations; FDC SC: fixed-dose combination of pertuzumab and trastuzumab for subcutaneous use; PPQ: Patient Preference Questionnaire; QoL: quality of life; SAE: serious adverse event; TASQ-IV/SC: Therapy Administration Satisfaction Questionnaire-intravenous/subcutaneous



Study Design

Description of Study

This is a Phase II, randomized, multi-centre, multinational, open-label, cross-over study in adult patients who have completed neoadjuvant chemotherapy with neoadjuvant Perjeta and Herceptin and have undergone surgical treatment of HER2+ EBC. An overview of the study design is provided in the figure below. A Schedule of Activities is provided in Appendix 2.

Study Schema

Abbreviations: IV: intravenous; P+H: Perjeta + Herceptin; FDC SC: subcutaneously administered fixed-dose combination of pertuzumab and trastuzumab; HCPQs: Healthcare Professional Questionnaires; PPQ: Patient Preference Questionnaire; SC subcutaneous; TASQ: Therapy Administration Satisfaction Questionnaire

Eligibility will be assessed within a 28-day screening period. Eligible patients will be enrolled and randomly allocated in a 1:1 ratio to treatment Arm A (P+H IV followed by pertuzumab and trastuzumab FDC SC) or treatment Arm B (FDC SC followed by P+H IV). Patients will be stratified according to neoadjuvant chemotherapy regimen (anthracyclines + taxanes vs. carboplatin + taxanes vs. taxanes only), neoadjuvant treatment response (pathologic complete response [pCR] vs. non-pCR) and hormone receptor status (oestrogen receptor [ER]-positive and/or progesterone receptor [PgR]-positive vs. ER-negative and PgR-negative). Study treatment will be initiated ≥ 2 weeks from breast cancer surgery but ≤ 9 weeks from the last administration of systemic neoadjuvant therapy and will be administered on Day 1 of each 3-week treatment cycle. No adjuvant chemotherapy is allowed after surgery, however, adjuvant hormone and/or radiation therapy are allowed.

Patients randomized to Arm A will receive P+H IV for three treatment cycles followed by pertuzumab and trastuzumab FDC SC for three treatment cycles. Patients randomized to Arm B will receive pertuzumab and trastuzumab FDC SC for three treatment cycles followed by P+H IV for three treatment cycles. This period of 3+3 cycles in both treatment arms constitutes the study Treatment Cross-over Period.

The 6 study treatment cycles of pertuzumab and trastuzumab FDC SC and P+H IV received during the Treatment Cross-over Period and P+H treatment cycles received in the neoadjuvant setting prior to study entry will be considered part of the total 18 anti-HER2 treatment cycles planned for all study patients. Following completion of the Treatment Cross-over Period, patients will enter the Treatment Continuation Period wherein they will receive the remaining anti-HER2 treatment cycles required to complete their 18 planned cycles unless disease recurrence, unacceptable toxicity or patient withdrawal from treatment necessitates early treatment cessation. Study treatment during this period will be either P+H IV or pertuzumab and trastuzumab FDC SC as selected by the patient at the end of the Treatment Cross-over Period.

Patients who, by the investigator's assessment, cannot tolerate pertuzumab and trastuzumab FDC SC or P+H IV may be allowed to receive P+H IV or pertuzumab and trastuzumab FDC SC, respectively, for their remaining planned anti-HER2 treatment cycles. The investigator must obtain approval from the Medical Monitor to switch study treatment.

Patient preference will be assessed based on the Patient Preference Questionnaire (PPQ) (administered following treatment administration on Day 1, Cycle 6 of the Treatment Cross-over Period). Treatment satisfaction will be assessed based on the Therapy Administration Satisfaction Questionnaire (TASQ) (administered following treatment administration on Day 1 of Cycles 3 and 6 of the Treatment Cross-over Period). Healthcare professionals will record their perception of time/resource use and convenience of treatment administration completing the Healthcare Professional Questionnaires (HCPQs). Perception of time use will be captured during the Treatment Cross-over Period and perception of convenience will be captured after administration of each patient's treatment Cycle 6. 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 baseline, Cycle 3, Cycle 6, and the end of study treatment visits as well as at 18 months, 2 years, and 3 years from randomization. The study questionnaires are provided in Appendix 2 and Appendix 3 of the protocol.

Patients will be assessed for safety by regular evaluation of adverse events (AEs), vital signs, routine clinical laboratory tests (haematology, blood chemistry) and left ventricular ejection fraction (LVEF) assessments; and by physical examinations. Adverse events will be reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0). Efficacy will be assessed based on investigator-evaluated disease status determined according to assessments conducted per institutional practice or according to the American Cancer Society / American Society of Clinical Oncology (ACS/ASCO) Breast Cancer Survivorship Care Guideline [Runowicz et al. 2016, see Appendix 4 of the protocol].

Patients will undergo an End of Treatment Visit approximately 28 days after completing study treatment and will enter the Follow-up Period wherein they will be followed for safety, disease status, survival and HRQoL (via the EORTC QLQ-C30) for three years from the date the last patient is randomized.

Patients who withdraw from the study following randomization will not be replaced. Patients can be screened for the study more than once.

Number of Patients

Approximately 140 patients will be randomized in the study to obtain at least 126 evaluable patients.

Target Population

The target population will consist of adult patients with HER2+ EBC who have received neoadjuvant Perjeta and Herceptin, and have completed neoadjuvant chemotherapy and subsequently undergone surgery for their breast cancer.

Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-specific criteria

- Female or male with histologically confirmed, HER2+ inflammatory, locally advanced or early-stage breast cancer who have received neoadjuvant Perjeta + Herceptin and have completed neoadjuvant chemotherapy and subsequently undergone surgery for their breast cancer.

  Note: The neoadjuvant chemotherapy regimen (including type and sequencing of selected agents) and the number of neoadjuvant Perjeta and Herceptin treatment cycles are at the discretion of the treating physician and patient. Subcutaneously administered Herceptin may have been used in the neoadjuvant setting. The use of any trastuzumab biosimilars in the neoadjuvant setting is not allowed.
- HER2+ breast cancer assessed at the local laboratory prior to initiation of neoadjuvant therapy. HER2+ status must be determined based on breast biopsy material obtained prior to

neoadjuvant treatment and is defined as 3+ by immunohistochemistry (IHC) and/or positive by HER2 amplification by *in situ* hybridization (ISH) with a ratio of ≥ 2 for the number of HER2 gene copies to the number of chromosome 17 copies

- Hormone receptor status of the primary tumour determined by local assessment. Hormone receptor status may be either positive (i.e. ER-positive and/or PgR-positive) or negative (i.e. ER-negative and PgR-negative)
- Completed all neoadjuvant chemotherapy and surgery. Adjuvant radiotherapy may be planned or ongoing at study entry and adjuvant hormone therapy is allowed during the study. Note that study treatment cannot be initiated within < 2 weeks of surgery but must be initiated ≤ 9 weeks from the last administration of systemic neoadjuvant therapy.
- No evidence of residual, locally recurrent or metastatic disease after completion of surgery. Patients with clinical suspicion of metastases must undergo radiological assessments per institutional practice to rule out distant disease.
- Wound healing after breast cancer surgery adequate per investigator's assessment to allow initiation of study treatment within ≤ 9 weeks of last systemic neoadjuvant therapy
- No adjuvant chemotherapy planned. Note that adjuvant hormonal treatment is allowed during the study.

General criteria

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group performance status 0 or 1
- Intact skin at planned site of subcutaneous (SC) injections (thigh)
- LVEF ≥ 55% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) within 28 days of study randomization
- No major surgical procedure unrelated to breast cancer within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of <1% per year, or 2 effective non-hormonal contraceptive methods during the study treatment periods and for 7 months after the last dose of study treatment. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she 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). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  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.

  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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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

  With female partners of childbearing potential or pregnant female partners, men 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. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.
- A negative serum pregnancy test must be available prior to randomization for women of childbearing potential (defined as post-menarchal, has not had ≥ 12 continuous months of amenorrhea with no identified cause other than menopause, and has not undergone surgical sterilization [removal of ovaries and/or uterus])

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

Cancer-specific criteria

- Stage IV (metastatic) breast cancer
- Current or prior history of active malignancy (other than current breast cancer) within the last five years. Appropriately treated non-melanoma skin cancer; *in situ* carcinomas, including cervix, colon, or skin; or Stage I uterine cancer within the last five years are allowed.

  A patient with previous invasive non-breast cancer is eligible provided he/she has been disease free for more than five years.
- Previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy [selective oestrogen receptor modulators, aromatase inhibitors], and antitumor vaccines) for treatment or prevention of breast cancer, except neoadjuvant Perjeta, Herceptin and chemotherapy for current breast cancer

General criteria:

- Investigational treatment within four weeks of enrolment
- Serious cardiac illness or medical conditions including, but not confined to, the following:
  - History of NCI CTCAE v4.0 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 randomization
  - Poorly controlled hypertension (e.g., systolic > 180 mmHg or diastolic > 100 mmHg)

- 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., hypokalaemia, hypomagnesemia, hypocalcaemia), or family history of sudden unexplained death or long QT syndrome
- Inadequate bone marrow function, defined by any of:
  - Absolute neutrophil count < 1.5 x 10^9/L
  - Platelet count < 100 x 10^9/L
  - Haemoglobin < 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
- Inadequate renal function with serum creatinine > 1.5 x ULN
- Current severe, uncontrolled systemic disease that may interfere with planned treatment (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound-healing disorders)
- Pregnant or breastfeeding, or intending to become pregnant during the study or within seven months after the last dose of study treatment. Women of childbearing potential must have a negative serum pregnancy test result within seven days prior to initiation of study treatment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in, and completion of, the study
- Known active liver disease, for example, active viral hepatitis infection (i.e., hepatitis B or hepatitis C), autoimmune hepatic disorders, or sclerosing cholangitis
- Concurrent, serious, uncontrolled infections, or known infection with human immunodeficiency virus (HIV)
- Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins
- Current chronic daily treatment with corticosteroids (dose > 10 mg methylprednisolone or equivalent excluding inhaled steroids)

End of Study

The end of the study is defined the Last Patient, Last Visit (LPLV) which will occur three years after the last patient is randomized or the date at which the last data point required for the final statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

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

Length of Study

The study is estimated to last approximately 4 years, based on a recruitment period of up to 10 months and 3 years of follow-up after the last patient is randomized.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are pertuzumab and trastuzumab FDC SC, Perjeta IV, and Herceptin IV.

Test Product (Investigational Drug)

Pertuzumab and trastuzumab FDC SC is given as a fixed dose (i.e. non-weight based). Pertuzumab and trastuzumab FDC SC will be provided in a loading dose configuration and a maintenance dose configuration. The 15 mL loading dose consists of 1200 mg pertuzumab and

600 mg trastuzumab. The 10 mL maintenance dose consists of 600 mg pertuzumab and 600 mg trastuzumab. Patients who have had ≥ 6 weeks since their last neoadjuvant dose of Perjeta or Herceptin at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations. All pertuzumab and trastuzumab FDC SC doses are administered by SC injection over 5 – 8 minutes at a rate of ≤ 2 mL/min with hand-held syringe to the thigh on Day 1 of each 3-week treatment cycle. Patients should be monitored for 30 minutes after their first pertuzumab and trastuzumab FDC SC dose administration regardless of whether a loading dose is required. Patients should be monitored for 10 - 15 minutes following subsequent administrations. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements.

Comparator (Active Control)

Perjeta IV is administered at a dose of 840 mg (loading dose) or 420 mg (maintenance dose) on Day 1 of each 3-week treatment cycle and should be administered before Herceptin IV. Patients who have had ≥ 6 weeks since their last neoadjuvant dose of Perjeta at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations. Perjeta 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. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements. The observation period should be completed prior to the subsequent Herceptin IV infusion.

Herceptin IV is administered at a dose of 8 mg/kg (loading dose) or 6 mg/kg (maintenance dose) on Day 1 of each 3-week treatment cycle. Patients who have had ≥ 6 weeks since their last neoadjuvant dose of Herceptin at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations. Herceptin IV loading dose (if required) will be administered as an infusion over approximately 90 (± 10) minutes after which the patient 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. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

Primary Analysis

The primary objective of this study is to evaluate patient preference for pertuzumab and trastuzumab FDC SC based on the proportion of patients indicating an overall preference for pertuzumab and trastuzumab FDC SC based on Question 1 of the PPQ. Question 1 of the PPQ is as follows: “All things considered, which method of administration did you prefer?”.

The primary endpoint will be analysed for the intent-to-treat (ITT) population and for the modified ITT (mITT) population. The mITT population will include all patients who received at least one dose by both SC and IV routes of administration during the Treatment Cross-over Period and subsequently answered at least Question 1 of the PPQ.

A point estimate with associated 95% confidence interval (CI) for the proportion of patients who preferred pertuzumab and trastuzumab FDC SC will be calculated for the mITT and ITT populations.

Analysis of the primary study endpoint will take place when all patients have completed their last treatment administration during the Treatment Cross-over Period.

Determination of Sample Size

The binary primary endpoint (the proportion of patients who express a preference for pertuzumab and trastuzumab FDC SC) will be estimated with associated two-sided 95% CI.

Assuming a rate of 70% of patients preferring pertuzumab and trastuzumab FDC SC and aiming at a distance from the estimated proportion to the CI limits of approximately ± 8%, a total

of 126 patients are needed for the evaluation of preference. Hence, the observed rate of 70% of patients preferring pertuzumab and trastuzumab FDC SC could be estimated to be within 61.9% and 78.4% with a probability of 95%.

To allow for 10% of the patients not providing an evaluable preference assessment, approximately 140 patients are targeted to be randomized into the study.

Interim Analysis

An interim analysis will be conducted to support a planned regulatory filing for FDC, which will consist of a subset of the analyses planned for the primary analysis. The results of this interim analysis will be evaluated by a Sponsor's Internal Monitoring Committee. Further details will be specified in the Statistical Analysis Plan.

Appendix 2
Schedule of Assessments

	Screening	Baseline	Treatment Cross-over Period						Treatment Continuation Period [a]			End of Treatment Visit [b]	Follow-up Period [c]
Study Cycle			1	2	3	4	5	6	7	11 [d]	15 (or last treatment cycle) [e]		
Day	–28 to –1	–7 to –1	1	1	1	1	1	1	1	1	1	≤ 28 days from last study dose	
Informed consent [f]	x												
Medical history and demographics	x												
Collection of pathology reports [g]	x												
Complete physical examination [h, i]	x					x			x				x [i]
Limited physical examination [h, i]			x	x	x		x	x		x	x	x	
Vital signs [j]	x		x			x			x			x	
ECOG Performance Status [h]		x	x			x			x	x	x	x	
Weight [h, k]	x		x	x	x	x	x	x	x	x	x	x	
Height	x												

	Screening	Baseline	Treatment Cross-over Period						Treatment Continuation Period [a]			End of Treatment Visit [b]	Follow-up Period [c]
Study Cycle			1	2	3	4	5	6	7	11 [d]	15 (or last treatment cycle) [e]		
Day	–28 to –1	–7 to –1	1	1	1	1	1	1	1	1	1	≤ 28 days from last study dose	
Investigator assessment to exclude residual / recurrent or metastatic disease as per institutional practice	x												
Clinical breast examination [l]	x		x			x			x	x	x	x	x [l]
Electrocardiogram	x												
LVEF [m]	x					x			x	x		x	x [m]
Haematology / limited biochemistry [n]	x		x			x			x	x	x	x	
Pregnancy test [o]		x				x			x [o]	x [o]	x [o]	x	x [o]
Adverse events [p]	x	x	Collected on an ongoing basis										x [p]
Concomitant medication [q]		x	Collected on an ongoing basis										x [q]
PPQ [r]								x					
TASQ-IV [s]					***Arm A*** *only*			***Arm B*** *only*					

	Screening	Baseline	Treatment Cross-over Period						Treatment Continuation Period [a]			End of Treatment Visit [b]	Follow-up Period [c]
Study Cycle			1	2	3	4	5	6	7	11 [d]	15 (or last treatment cycle) [e]		
Day	–28 to –1	–7 to –1	1	1	1	1	1	1	1	1	1	≤ 28 days from last study dose	
TASQ-SC [s]					***Arm B*** *only*			***Arm A*** *only*					
EORTC QLQ-C30 [t]			x		x			x			x		x [t]
HCPQ-Treatment Room [u]			x	x	x	x	x	x					
HCPQ-Drug Preparation Area [u]			x	x	x	x	x	x					
Bilateral mammogram (or other breast imaging method per institutional practice) [v]												x	
Assessments for breast cancer recurrence			Per institutional practice or the ACS / ASCO Breast Cancer Survivorship Care Guideline [see Appendix 4 of the protocol]										
Assessments for non-breast primary cancers			Per institutional practice										
Survival													x
P+H IV			***Arm A*** *only*	***Arm A*** *only*	***Arm A*** *only*	***Arm B*** *only*	***Arm B*** *only*	***Arm B*** *only*					

	Screening	Baseline	Treatment Cross-over Period						Treatment Continuation Period [a]			End of Treatment Visit [b]	Follow-up Period [c]
Study Cycle			1	2	3	4	5	6	7	11 [d]	15 (or last treatment cycle) [e]		
Day	–28 to –1	–7 to –1	1	1	1	1	1	1	1	1	1	≤ 28 days from last study dose	
Pertuzumab and trastuzumab FDC SC			*Arm B only*	*Arm B only*	*Arm B only*	*Arm A only*	*Arm A only*	*Arm A only*					
P+H IV or pertuzumab and trastuzumab FDC SC									every cycle from C7 until the end of EBC treatment [w]				

ALT = alanine aminotransferase; ANC = absolute neutrophil count; ACS/ASCO: American Cancer Society / American Society of Clinical Oncology; AST = aspartate aminotransferase; EBC= early breast cancer ; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FDC SC = fixed-dose combination for subcutaneous administration; FU = follow-up; HCPQ = Healthcare Professional Questionnaire; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MUGA = multi-gated acquisition; PPQ = Patient Preference Questionnaire; P+H IV = Perjeta intravenous + Herceptin intravenous; TASQ-IV/SC = Therapy Administration Satisfaction Questionnaire for Intravenous Administration / Subcutaneous Administration; WBC = white blood cell.

Notes 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.

a. Either pertuzumab and trastuzumab FDC SC or P+H IV will be selected by the patient for study treatment during the Treatment Continuation Period. During this period, pertuzumab and trastuzumab FDC SC or P+H IV will be administered for the number of 3-weekly cycles calculated based on the number of Perjeta and Herceptin cycles received as neoadjuvant treatment prior to study entry and P+H IV and pertuzumab and trastuzumab FDC SC cycles (six total cycles) received during the Treatment Cross-over Period. A total of 18 cycles of anti-HER2 treatment

should be administered for EBC treatment unless disease recurrence, unacceptable toxicity or patient withdrawal from treatment necessitates early cessation of treatment. No specific investigations are required per protocol for Cycles 8-10 and Cycles 12-14 during the Treatment Continuation Period, although the PI may perform safety laboratory assessments or other tests per institutional practice (these results are not required to be reported in the eCRF). However, information on treatment administration will be collected, and new or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

b. End of Treatment Visit to be performed within 28 days (± 7 days) of the administration of the last dose of any study drug.

c. Study patients will be followed for at least three years from randomization. A follow-up visit should occur at least every six months during this period.

d. If study treatment Cycle 12 is planned as last study treatment cycle (i.e. corresponding to Cycle 18 of neo/adjuvant anti-HER2 treatment), all planned assessments may be delayed to study treatment Cycle 12

e. The number of the last treatment cycle in Treatment Continuation Period will depend on number of neoadjuvant cycles with Perjeta and Herceptin. A total of 18 cycles of HER2-targeted therapy should be administered over neo/adjuvant treatment (i.e. neoadjuvant cycles + Treatment Cross-over Period Cycles + Treatment Continuation Period cycles = 18 neo/adjuvant cycles).

f. 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.

g. Pathology reports from initial breast cancer diagnosis and from breast cancer surgery will be collected. Results of local HER2 and hormone receptor testing conducted prior to neoadjuvant therapy will also be collected.

h. Must be performed pre-dose on study treatment dosing days

i. Complete physical examinations should include physical measurements (body weight in kilograms and height in centimetres) 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 baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited physical examinations are symptom-directed and, in addition to the scheduled examinations indicated, may be conducted as clinically indicated. New or worsened clinically significant abnormalities observed post-baseline should be recorded as AEs on the Adverse Event eCRF. During the Follow-up Period, 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, see Appendix 4 of the protocol].

j. Vital signs (heart rate, blood pressure, temperature, respiration rate) will be taken before and after study treatment administration. Heart rate, blood pressure, and respiration rate should be obtained while the patient is seated.

k. Weight will be measured during screening and on Day 1 of each cycle prior to treatment administration. If variation of ≥ ± 10% compared with baseline occurs, Herceptin IV dosing should be recalculated. Weight at the time the Herceptin IV dose is recalculated will be considered as baseline for subsequent evaluations of degree of weight change with respect to Herceptin IV dose modification requirements.

l. Clinical breast examination should be performed to detect signs of residual disease / local recurrence prior to study entry and to detect locoregional relapse during the Treatment Cross-over and Treatment Continuation Periods, and at the End of Treatment Visit. During the Follow-up Period, clinical breast exams should be conducted in accordance with institutional practice or the ACS/ASCO Breast Cancer Survivorship Care Guideline [Runowicz et al. 2016, see Appendix 4 of the protocol].

m. LVEF may be assessed by ECHO or MUGA however the same method should be used throughout the study for each patient and should be performed and assessed by the same assessor where possible. During the study treatment periods, results of LVEF assessments must be reviewed prior to study treatment administration on the scheduled visit day. During the Follow-up Period, LVEF should be assessed at 6, 12, and 24 months after last study treatment or per institutional practice.

n. Haematology: haemoglobin, total WBC, ANC / neutrophils, platelet count. Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. Albumin should be measured at Screening for determining patient eligibility. Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN. During the treatment period, bloods for haematology / biochemistry may be taken within three days prior to study treatment administration.

o. Pregnancy testing is only required for women of childbearing potential: A woman of childbearing potential is 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). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements. Pregnancy tests must be performed via serum β-human chorionic gonadotropin (HCG) at baseline within seven days prior to first study treatment administration. Urine pregnancy tests should be repeated during the Treatment Cross-over and Treatment Continuation Periods at Cycle 4, Cycle 7, Cycle 11 and Cycle 15 (or at last treatment cycle), and as clinically indicated, with results available prior to study treatment administration, as well as at the End of Treatment Visit and at the Follow-up Visit until seven months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test.

p. Adverse event reporting period will continue up to seven months after the last dose of study drug. After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected. After initiation of study treatment, all AEs regardless of relationship to study drug will be reported until 28 days after the last dose of study drug. Between 28 days and 7 months after the last dose of study drug, drug-related SAEs, AEs of special interest, heart failure, pregnancies, non−breast-related second primary malignancies and deaths, should continue to be collected. After the end of the adverse event reporting period (defined as seven months after the last dose of study drug), drug-related SAEs, AEs of special interest, heart failure, non−breast-related second primary malignancies and deaths, should continue to be collected should be collected.

q. All concomitant medications used by the patient from seven days prior to initiation of study drug until the End of Treatment Visit should be reported. After the End of Treatment Visit and until the end of the study, only medications used for the treatment of cancer will be reported.

r. The Patient Preference Questionnaire (PPQ) must be completed following study treatment administration on Day 1 of Cross-over Treatment Period Cycle 6. Patients who discontinued study treatment prior to study treatment Cycle 6 should complete the questionnaire at the time of

discontinuation as long as they have received at least one dose of pertuzumab and trastuzumab FDC SC, Perjeta IV and Herceptin IV post-randomization.

s. Patients in Arm A will complete the Therapy Administration Satisfaction Questionnaire for IV administration (TASQ-IV) immediately following study treatment administration on Day 1 of Cycle 3 of the Treatment Cross-over Period and the Therapy Administration Satisfaction Questionnaire for SC administration (TASQ-SC) immediately following study treatment administration on Day 1 of Cycle 6 of the Treatment Cross-over Period. Patients in Arm B will complete the TASQ-SC and TASQ-IV immediately following study treatment administration on Day 1 of Cycle 3 and 6 of the Treatment Cross-over Period respectively. Patients who switch study treatment due to investigator-assessed lack of tolerance should complete the TASQ corresponding to the study treatment they cannot tolerate prior to switching treatment (i.e. after the decision to change study treatment has been approved by the Medical Monitor and before receiving the next study treatment).

t. During the study treatment periods, patients must complete the EORTC QLQ-30 before the patient and clinician receives any information on disease status and prior to treatment administration on the scheduled visit day. During the Follow-up Period, the EORTC QLQ-30 must be completed at 18 months, 2 years, and 3 years from randomization.

u. Each Healthcare Professional Questionnaire (HCPQ) will be completed by the applicable HCP after each study treatment preparation and/or administration for each patient. Applicable HCPs are described in each of the questionnaires (HCPQ-Treatment Room, HCPQ-Drug Preparation Area). Instructions for which questions should be completed in each questionnaire at each timepoint are indicated in the introduction to each questionnaire.

v. Mammograms conducted at the time of diagnosis (before initiation of the neoadjuvant treatment) as well as pre-surgery (if performed) will be collected. Mammograms collected and/or conducted for the study (including pre-neoadjuvant treatment, pre-surgery, and study Follow-up Period evaluations) can be replaced by another conventional imaging method such as magnetic resonance imaging (MRI) or ultrasound per institutional practice at the investigator's discretion, but the same method of assessment must be used for each evaluation for an individual patient. If a mammogram (or acceptable alternative breast imaging evaluation) has been conducted as part of routine care within four months prior to the End of Treatment Visit, it may be used in lieu of the End of Treatment Visit evaluation.

w. After completion of the Treatment Cross-over Period, participating patients will select the study treatment formulation (P+H IV or pertuzumab and trastuzumab FDC SC) to complete their 18 cycles of neo/adjuvant HER2-targeted treatment. The number of study treatment cycles administered during the Treatment Continuation Period required to complete a total of 18 of neo/adjuvant HER2-targeted treatment will be calculated based on the sum of number of P+H cycles received in neoadjuvant treatment (before study entry) plus 6 cycles administered in the Treatment Cross-over Period.