Official Title: A Phase III, Randomized, Multicenter, Open-Label, Two-Arm Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of Subcutaneous Administration of the Fixed-Dose Combination of Pertuzumab and Trastuzumab + Chemotherapy in Patients With HER2-Positive Early Breast Cancer

NCT Number: NCT03493854

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STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE III, RANDOMIZED, MULTICENTER, OPEN-LABEL, TWO-ARM STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB + CHEMOTHERAPY IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**
PROTOCOL NUMBER:	WO40324
STUDY DRUG:	Fixed-Dose Combination (FDC) of pertuzumab and trastuzumab for subcutaneous administration (RO7198574)
VERSION NUMBER:	3
IND NUMBER:	131009
EUDRACT NUMBER:	2017-004897-32
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted], PhD.
DATE FINAL:	See electronic date stamp below

Date and Time(UTC)	Reason for Signing	Name
23-Aug-2019 08:32:27	Company Signatory	[redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan (SAP) for Study WO40324 (FeDeriCa) has been amended to incorporate the following changes.

VERSION 2:

Two changes concerning exploratory efficacy endpoints:

- Removing Per Protocol PK analysis population from exploratory efficacy analysis Section 4.5.5.

  This line was to be removed in previous version but due to error was retained in the final version 1. This was changed in version 2 to align with initial strategy described in section 4.5.
- Addition of text 'the non-inferiority margin' to make the clear that the pre-established non-inferiority margin is -12.5% (absolute percentage points).

VERSION 3:

- Addition of two new exclusion criteria in section 4.1.1 Per Protocol PK analysis population:
  - If pre-dose and post-dose samples were switched
  - Assay error impacting C_{trough} measurement.

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

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1. BACKGROUND

Study WO40324 is a global Phase III study to investigate pharmacokinetics (PK), efficacy, and safety of the fixed-dose combination (FDC) of pertuzumab and trastuzumab in combination with chemotherapy in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (EBC) in the neo-adjuvant/adjuvant setting.

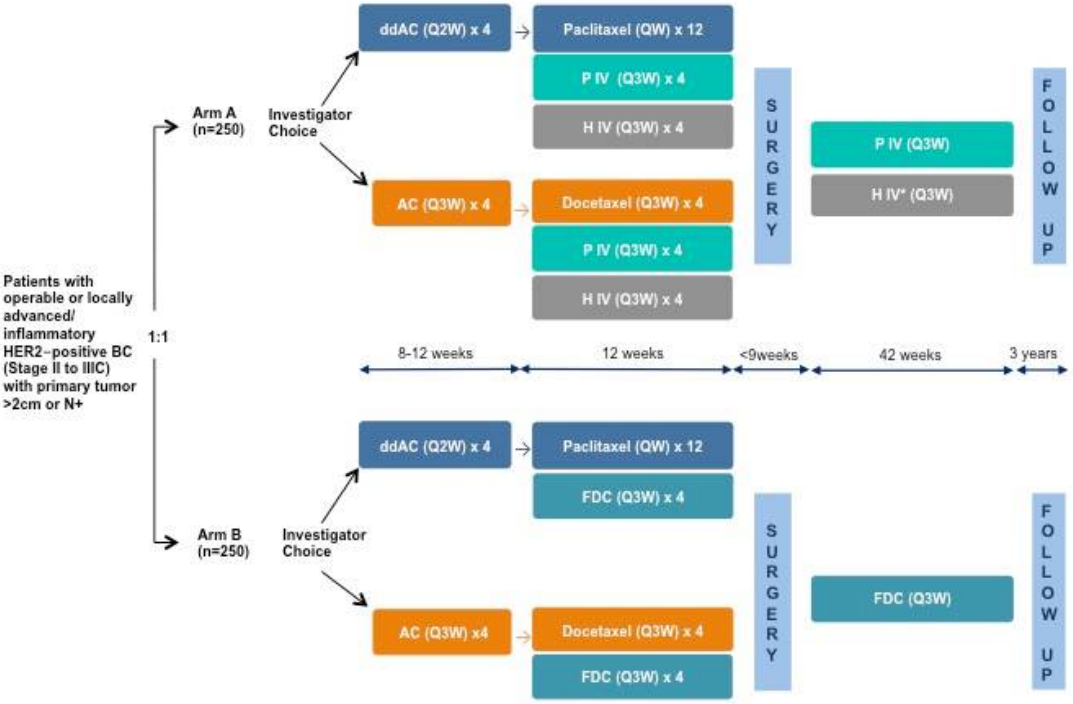
The purpose of this Statistical Analysis Plan (SAP) is to provide details of the proposed analyses of this study for regulatory submissions.

2. STUDY DESIGN

WO40324 is a two-arm, open-label, multicenter, randomized study (see Figure 1). The study will enroll patients with HER2-positive breast cancer consistent with the indication for treatment with neo-adjuvant Perjeta and Herceptin in combination with chemotherapy in routine clinical practice and as recommended in local guidelines.

The study is designed to assess PK non-inferiority in pertuzumab C_{trough} for patients treated with the FDC compared to treatment with Perjeta® (pertuzumab) and Herceptin® (trastuzumab) intravenous (IV) formulations.

Figure 1 : Study Design Schema



*Herceptin SC may be used in the adjuvant period from Cycle 9 and onwards, at the discretion of the investigator.
AC = doxorubicin and cyclophosphamide; ddAC = dose-dense doxorubicin and cyclophosphamide; FDC = Fixed-dose Combination of pertuzumab and trastuzumab SC; H = Herceptin; IV = intravenous; N = Node; P = Perjeta; SC=subcutaneous.
Note: For Cohorts A and B, the doses of AC are doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC is given Q3W; ddAC is given Q2W). The dose of paclitaxel is 80 mg/m^2 (given QW for 12 weeks). The starting dose of docetaxel is 75 mg/m^2 in Cycle 5 (the first docetaxel cycle) and then 100 mg/m^2 at the discretion of the investigator for Cycles 6-8, if no dose-limiting toxicity occurs (given every 3 weeks).

Approximately 500 patients with HER2-positive, operable or locally advanced/inflammatory breast cancer with a tumor size of either >2 cm in diameter or node-positive will be randomized to one of the following treatment arms in a 1:1 ratio:

- **Arm A** (Perjeta IV + Herceptin IV): Patients will receive 8 cycles of neo-adjuvant chemotherapy. This will include 4 cycles of dose-dense doxorubicin (Adriamycin®) plus cyclophosphamide (ddAC) every two weeks (Q2W; given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel Q1W for 12 weeks or 4 cycles of doxorubicin (Adriamycin®) plus cyclophosphamide (AC) every three weeks (Q3W) followed by docetaxel Q3W for 4 cycles. Perjeta + Herceptin will be given IV for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, patients will undergo surgery. Thereafter, patients will receive an additional 14 cycles of Perjeta IV and Herceptin IV for a total of 18 cycles. One year of HER2-targeted therapy without any delays would encompass 18 cycles.

After surgery (from Cycle 9 onwards), patients in Arm A are allowed to switch from Herceptin IV to Herceptin subcutaneous (SC), at the discretion of the investigator, in the countries where Herceptin SC is routinely used.

- **Arm B** (FDC of pertuzumab and trastuzumab for SC administration): Patients will receive 8 cycles of neoadjuvant chemotherapy. This will include 4 cycles of ddAC

Q2W (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel Q1W for 12 weeks or 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. FDC will be given SC for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neo-adjuvant therapy, patients will undergo surgery. Thereafter, patients will receive an additional 14 cycles of the FDC for a total of 18 cycles. One year of HER2-targeted therapy without any delays would encompass 18 cycles.

The investigator will select one of the two protocol-approved neoadjuvant chemotherapy regimens with which to treat the patient. Once the investigator's choice of chemotherapy has been made and eligibility confirmed, the patient will be randomized to one of the two treatment arms.

After the end of the study treatment, patients will be followed for safety and efficacy for 3 years (36 months) after the last patient's last dose. The end of the study is defined as the date when the last patient last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient (or when all patients have died or the trial is terminated by the Sponsor, whichever is earliest).

The total length of the study, from screening of the first patient to the end of the study is expected to be approximately 5.5 years.

Endpoints and objectives are listed in the Protocol Synopsis, see Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.1 DETERMINATION OF SAMPLE SIZE

The study is designed to have at least 80% power to demonstrate non-inferiority of the Cycle 7 (i.e., pre-dose Cycle 8) pertuzumab serum C_{trough} from pertuzumab SC within FDC to the Perjeta IV formulation in patients with HER2-positive EBC.

PK sample size calculations are based on the coefficient of variation (CV)% for the C_{trough} of trastuzumab observed from previous studies in metastatic breast cancer and EBC patients after Q3W treatment. With a CV of 60% assumed, a minimum of 130 patients per arm (i.e., a total of 260 patients) is needed to demonstrate C_{trough} non-inferiority with a power of 80% if the true means of the two formulations do not differ by more than 5%. An additional 240 patients will also be recruited to provide a substantial database to assess total pathological complete response (tpCR) and safety profile comparability. Therefore, a total of approximately 500 patients (~250 per arm) will provide a sufficient sample size to test the primary PK hypothesis and also assess efficacy and safety profile comparability.

2.2 ANALYSIS TIMING

The primary analysis for PK will occur when all patients have completed neoadjuvant therapy (i.e., completed Cycle 8) and had surgery. At this timepoint, secondary endpoints of trastuzumab C_{trough}, exploratory PK (where available), tpCR (and the exploratory pCR), Immunogenicity, Biomarkers (as available) and safety will also be analyzed.

A final analysis will occur when all patients have completed 36 months of treatment free-follow up. At this timepoint, invasive disease-free survival (iDFS), iDFS including second primary non-breast cancer, event-free survival (EFS), EFS including second primary non-breast cancer, distant recurrence-free interval (DRFI), overall survival (OS) and safety will be analyzed. Exploratory analyses for PK (those not performed at the primary analysis) will also be assessed.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Randomization will occur through an interactive voice/web-based response system (IxRS). On verification of inclusion and exclusion criteria, eligible patients will be randomized using the method of stratified permuted blocks in a 1:1 ratio to receive either treatment Arm A or Arm B. Patients will be stratified according to the following factors:

- Hormonal Receptor Status (based on central assessment):
  - Estrogen receptor (ER)-positive or progesterone receptor (PgR)-positive
  - ER-negative and PgR-negative
- Clinical stage at presentation:
  - Stage II−IIIA
  - Stage IIIB−IIIC
- Type of chemotherapy:
  - ddAC followed by paclitaxel
  - AC followed by docetaxel

A patient may only be randomized once in this trial. Patients randomized into the study will not be replaced. Patients who choose to withdraw after screening but before randomization will be replaced.

Review of dummy randomization lists along with User Acceptance Testing (UAT) within the IxRS system will be performed to ensure the randomization procedure is set up and performed correctly.

3.2 DATA MONITORING

An Independent Data Monitoring Committee (iDMC) will be established to monitor and evaluate patient safety throughout the study. The iDMC members will be external to Roche and independent of the trial. The iDMC will be comprised of a fixed number of permanent members with experience in clinical studies in oncology and will include at least one statistician. The iDMC will follow a charter that outlines their roles and responsibilities and ability to make recommendations regarding continuation of the study to ensure integrity and viability of the trial, as well as acceptable risk to patients in the trial. The iDMC will be responsible for monitoring the safety of patients in the study and will make recommendations to the Sponsor through the Data Review Board (DRB) regarding the conduct of the study, including study continuation as planned or with protocol amendment or early discontinuation of the study for excessive toxicity.

The first iDMC meeting will approximately take place after the first 50 patients have been randomized into the study and have completed their full course of neo-adjuvant therapy (8 cycles). Additional review meetings are planned to occur when approximately 200 and 500 patients have been randomized and have completed their full course of neoadjuvant therapy. Thereafter, further review meetings will take place approximately every 6 months until the primary analysis. The iDMC schedule may be modified based on the recommendation of its members or request by the Sponsor. The operating procedures for the meetings will be detailed in the iDMC charter.

The Study Management Team is, by definition, unblinded given the open-label nature of this study. However, to further protect the integrity of the study, any treatment assignment information, such as the randomization file from the IxRS and PK data, will be withheld from the Sponsor until the primary analysis. Review of data for safety purposes will not be reviewed at an aggregate level prior to the primary analysis.

For data reviews by the iDMC, the independent data co-ordinating center (iDCC) will prepare the data packages for safety review, and will create an unblinded data package for the iDMC review and a blinded package for non-IDMC member review. Further details will be written into the iDMC charter.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 Per Protocol PK Analysis Population

The primary analysis will be performed in the Per Protocol PK analysis population. Patients will be assigned to treatment groups as treated.

The Per Protocol PK analysis population will include all patients enrolled who adhered to the protocol. Exclusions from the Per Protocol PK analysis population will be made for the following reasons: patients are missing the C_{trough} pre-dose Cycle 8 PK sample, patients with a C_{trough} sample collected with at least 2 days deviation from the planned

date on Day 21 (i.e., before Day 19 or after Day 23), patients given a dose amount that deviates from the planned dose by > 20% within 3 cycles (from Cycle 5), patients with a dose delay of more than 7 days, a subcutaneous injection site other than thigh is used, if pre-dose and post-dose samples were switched and assay error impacting C_{trough} measurement. Excluded cases will be documented, including the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

4.1.2 Intent-to-Treat population

Additional analyses will be performed in the intent-to-treat (ITT) population. The ITT population is defined as all randomized patients. Patients will be assigned to treatment groups as randomized by the IxRS.

4.1.3 Safety Analysis Population

The safety analysis population will include all patients who receive at least one dose of study medication (i.e., chemotherapy, Perjeta IV, Herceptin IV, Herceptin SC or the FDC). Patients who do not receive any amount of their study medication (i.e., chemotherapy, Perjeta IV, Herceptin IV, Herceptin SC or the FDC) will be excluded from the safety-evaluable population. Patients will be assigned to treatment groups as treated.

Patients in Arm A, who switch to Herceptin SC after surgery, will be analyzed as a separate subset of Arm A.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients who enroll, discontinue (from treatment and/or study), or complete the study will be summarized. Reasons for patient discontinuations from the study treatment and from the study will be listed and summarized. Enrollment, study treatment administration, and major protocol deviations will be evaluated for their potential effects on the interpretation of study results.

For safety-evaluable patients, study drug administration and dose modifications data will be tabulated or listed by cohort, using descriptive statistics to summarize the total doses where applicable.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

The evaluation of treatment group comparability between the two treatment arms will include summaries of demographics, medical history, concomitant medication and a summary of the randomization stratification factors.

Demographic and baseline characteristics will be summarized using descriptive statistics (e.g., means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate). Summaries will be presented by treatment group and separated where relevant into the neo-adjuvant period, adjuvant period and follow up period. Where applicable for the neo-adjuvant period, summaries

will be presented by treatment arm and chemotherapy regimen. Patients in the adjuvant period, who switch from Herceptin IV to Herceptin SC will be presented under two summary tables: overall whereby these patients even though switch will remain under a treatment label of Pertuzumab IV + Herceptin IV, and then where applicable for safety a second table whereby these patients are counted only from their switch onwards, under Pertuzumab IV + Herceptin SC. Frequency counts will be presented by randomized treatment arm for categorical variables.

4.4 PRIMARY ANALYSIS

The primary endpoint of this study is observed pertuzumab trough concentration (C_{trough}) at Cycle 7 (i.e., the measured pre-dose concentration value at Cycle 8), following 3 cycles of Perjeta IV and Herceptin IV or FDC (pertuzumab and trastuzumab SC). Pertuzumab C_{trough} will be analyzed at the time of the primary analysis, which will occur after the last patient has completed (all) neo-adjuvant therapy and has undergone surgery.

The Per Protocol PK analysis population as described in Section 4.1.1 will be the primary analysis population used for this analysis.

The non-inferiority of the SC and IV dose of pertuzumab will be assessed by a one-sided testing procedure. The C_{trough}SC/C_{trough}IV GMR of the SC dose of pertuzumab relative to the IV dose will be estimated together with the two sided 90% CI based on the log-transformed trough concentration values.

The hypothesis to be tested for the primary endpoint, observed pertuzumab C_{trough}, is:

- H0: The SC dose is inferior to the IV dose (i.e., the C_{trough}SC/C_{trough}IV geometric mean ratio [GMR] of the SC dose of pertuzumab relative to the IV dose is not greater than 0.8) versus
- H1: The SC dose is non-inferior to the IV dose (i.e., C_{trough}SC/C_{trough}IV GMR of the SC dose of pertuzumab relative to the IV dose is equal or greater than 0.8).

The null hypothesis will be rejected and non-inferiority will be concluded if the lower bound of the 90% CI of the GMR is $\geq$ 0.8.A hierarchical testing procedure for key secondary endpoints (that is, for trastuzumab serum C_{trough}SC/C_{trough}IV) will be used to control the overall type I error rate at a one sided 5% significance level.

4.5 SECONDARY ANALYSES

For all secondary PK analyses the per protocol PK analysis population (see Section 4.1.1) will be used. The ITT population will be used for key secondary endpoint analyses such as, but not limited to, pCR, EFS, DFS and OS.

4.5.1 PK Analysis

The non-inferiority of the SC and IV dose of trastuzumab will be assessed using the same criteria as for the primary analysis (see Section 4.4) and will be tested in a

hierarchical order to adjust for multiple statistical testing and control the type I error at one sided 5% significance level.

The following hypotheses will be tested:

- H0: The SC dose is inferior to the IV dose (i.e., the C_{trough}SC/C_{trough}IV GMR of the SCdose of trastuzumab relative to the IV dose is not greater than 0.8) vs.
- H1: The SC dose is non-inferior to the IV dose (i.e., the C_{trough}SC/C_{trough}IV GMR of the SC dose of trastuzumab relative to the IV dose is equal or greater than 0.8).

The hierarchical testing procedure will follow the steps below:

1. Test the primary endpoint, Cycle 7 pertuzumab serum C_{trough}SC/C_{trough}IV, at a one-sided 5% significance level. If positive, continue to step 2; otherwise, stop.
2. Test the secondary endpoint, Cycle 7 trastuzumab serum C_{trough}SC/C_{trough}IV, at a one-sided 5% significance level.

The non-inferiority of the SC and IV dose of pertuzumab will be assessed by a one-sided testing procedure. The null hypothesis will be rejected and non-inferiority will be concluded if the lower bound of the 90% CI of the GMR is ≥ 0.8.

4.5.2 Efficacy Analyses

The following secondary endpoints will be analyzed outside of a hypothesis-testing framework and according to the methodology provided below.

Total pCR is defined as eradication of invasive disease in the breast and axilla; that is, ypT0/is ypN0, according to the local pathologists' assessment. Pathologic response to therapy is defined at the time of surgery, and the tpCR rate is the proportion of patients in the ITT population who achieve a tpCR. Rates of tpCR will be calculated in each treatment arm and will be assessed using the difference between FDC tpCR rate and IV tpCR rate and corresponding 95% Clopper-Pearson CIs. The difference between the FDC tpCR rate and IV tpCR rates along with corresponding 95% Hauck-Anderson CIs will also be calculated. The lower bound of the CI will reliably reflect the largest tpCR difference that can be considered unlikely. The observed tpCR difference and 95% CIs will form the basis of a discussion around the differences in efficacy that can be ruled out. See Table 1 for a range of possible tpCR differences and 95% CIs under various scenarios to demonstrate the precision for each outcome with the proposed sample size of N = 500. An assessment of tpCR will be analysed at the time of primary analysis.

Table 1 Precision for different tpCR rates (N=500)

PIV+HIV pCR rate	FDC SC pCR rate	Difference in tpCR rates	Lower 95% CI for difference	Upper 95% CI for difference
50%	45%	-5%	-13.96%	3.96%
50%	50%	0%	-8.98%	8.98%
50%	55%	5%	-3.96%	13.96%
55%	50%	-5%	-13.96%	3.96%
55%	55%	0%	-8.94%	8.94%
55%	60%	5%	-3.87%	13.87%
60%	55%	-5%	-13.87%	3.87%
60%	60%	0%	-8.81%	8.81%
60%	65%	5%	-3.69%	13.69%
65%	60%	-5%	-13.69%	3.69%
65%	65%	0%	-8.58%	8.58%
65%	70%	5%	-3.42%	13.42%

CI=Hauk-Anderson 95% Confidence Intervals; FDC=fixed-dose combination; H=Herceptin; IV=intravenous; P=Perjeta; pCR=pathological complete response; SC=subcutaneous; tpCR=total pathological complete response.

Note: The table above shows a range of possible tpCR differences under a number of scenarios to demonstrate the precision for each outcome. For example, if a 60% pCR rate is observed in both arms, i.e., a difference of 0%, with 250 patients per arm it can be ruled out with high probability that the true difference is ~9% , or that the SC tpCR rate is more than 9% lower than the IV pCR rate.

For the additional secondary time-to-event (TTE) endpoints, iDFS, iDFS including second primary non-breast cancer, EFS, EFS including second primary non-breast cancer, DRFI and OS (see Protocol Synopsis in Appendix 1 for definitions), the Kaplan-Meier approach will be used for analysis. Estimates of the proportion of patients who are event-free at landmark timepoints for each treatment cohort will be provided. The estimated hazard ratio and corresponding CI will also be obtained using stratified Cox regression models. Patients who are either without distant disease recurrence, alive or lost to follow-up for the respective endpoints will be censored at the date they were last known to be event free. Patients with no post-baseline assessments will be censored at the date of randomization plus 1 day. The TTE endpoints will not be analyzed at the time of the primary analysis, but will be analyzed at the final analysis.

4.5.3 Exploratory Endpoints - PK, pCR, Immunogenicty and Biomarker Endpoints

Exploratory analyses will be performed based on sufficient data, and is not limited to those listed here.

4.5.4 Exploratory PK Analyses

The exploratory PK analyses and modelling (see Section 6.5.1 in protocol synopsis) will include characterization of the pharmacokinetics of pertuzumab and trastuzumab following FDC SC administration. PK variables will be presented by listings and descriptive summary statistics including arithmetic mean, geometric mean, median, range, standard deviation and CV, and 95% confidence intervals. Modelling of the PK data may be performed using a population approach based on a model previously developed on a combined SC and IV dataset from the BO30185 study. The structural and statistical model will be defined using a non-linear mixed effect model (NONMEM). The model will be parametrized in terms of clearances and volumes, and the individual measures of exposure (i.e., C_{trough} and $AUC_{0-\tau}$) will be predicted from the final PK model.

These analyses will be assessed by the clinical pharmacology group and analysis details will be provided in a separate PK analysis plan.

4.5.5 Exploratory Efficacy Analyses

To further assess the tpCR endpoint, exploratory analyses will be conducted analyzing different definitions of pCR including:

- Breast pathological complete response (bpCR), defined as eradication of invasive disease in the breast (i.e., ypT0/is, ypNx)
- German Breast Group (GBG) pCR, defined as eradication of invasive and in situ disease in the breast and invasive disease in axilla (i.e., ypT0 ypN0)

Analysis methods will be the same as those for the secondary tpCR endpoint (see Section 4.5.2). The ITT population as defined in Section 4.1.3 will be used for analyses.

Additionally, tpCR (as per definition of the secondary endpoint, Section 4.5.2) will also be assessed with respect to non-inferiority for descriptive purposes, acknowledging this is not type-1 error (alpha) controlled. Non-inferiority in tpCR rate will be assessed using the criteria that the lower limit of the one-sided 97.5% confidence interval for the difference in tpCR rate using the continuity correction of Anderson and Hauck (1986) is above non-inferiority margin of -12.5% (absolute percentage points). The difference in pCR rate is defined as the tpCR rate in the SC pertuzumab arm minus the tpCR rate in the IV pertuzumab arm.

In the neoadjuvant period, clinical response will be analyzed and response will be assessed as complete response, partial response, stable disease, or progressive disease by the investigator as per routine clinical practice (see Section 4.5.12 in protocol). Clinical response rate prior to surgery will be summarized and reported. For patients who have clinical response assessed during neo-adjuvant therapy but not immediately prior to surgery, and patients who do not undergo surgery, the last recorded clinical response assessment will be considered in the analysis. Patients without any assessment of clinical response prior to surgery will be considered non-responders in the analysis.

4.5.6 Immunogenicity Analyses

The immunogenicity analysis population will consist of all patients with at least one anti-drug antibody (ADA) assessment, [redacted]. Patients will be grouped according to treatment received.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (post-baseline incidence) will be summarized by treatment group (see additional detail around baseline characterization and positive/negative status in protocol section 6.5.3). The relationship between ADA status and safety, efficacy, and PK endpoints will be analyzed and reported via descriptive statistics (as data allow). The relationship between neutralizing antibody (NAb) status and efficacy and PK will also be assessed (NAb is a subset of ADA positive patients).

[redacted]

4.5.8 Sensitivity Analyses

The analyses defined in Section 4.5.4 and Section 4.5.5 will serve as the sensitivity analyses.

4.5.9 Subgroup Analyses

For the primary endpoint of PK pertuzumab C_{trough}, there are no prespecified subgroup analyses planned.

Exploratory analyses will be performed for tpCR to assess whether magnitude of the effectiveness of FDC differs according to patient subgroups. Subgroup analyses will be performed for the randomization stratification factors using the categories defined in Section 3.1, as well as for other disease-or patient-related prognostic or predictive factors, such as but not limited to:

- Age: <65, ≥ 65
- Race: White; Black; Asian; Other

- Hormonal receptor status (per central lab): ER and/or PgR positive; ER/PgR negative
- Hormonal receptor status (per local lab): ER and/or PgR positive; ER/PgR negative
- Clinical stage at presentation: stage II-IIIA; stage IIIB-IIIC
- Type of chemotherapy: ddAC-weekly paclitaxel; AC-docetaxel
- Menopausal status at randomization: pre-menopausal; post-menopausal
- Histological grade at baseline: Grade 1; Grade 2; Grade 3
- Histological subtype: Invasive carcinoma of no special type (NST), Invasive lobular carcinoma, Invasive micropapillary carcinoma, Mucinous carcinoma, Apocrine carcinoma, Other

Subgroup analyses will be performed in an exploratory manner using forest plots with descriptive statistics summarizing tpCR rates and 95% CIs, by treatment arm.

4.6 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug and will be grouped according to actual treatment received: Arm A to Perjeta IV and Herceptin IV; Arm B to FDC of pertuzumab and trastuzumab (see Section 4.1.3 for population details).

Safety will be evaluated by the use of descriptive analyses of incidence and severity of adverse events (AEs) and serious adverse events (SAEs); laboratory test abnormalities; incidence of a symptomatic left ventricular systolic dysfunction (LVSD; otherwise referred to as heart failure), defined as the occurrence of symptomatic left ventricular ejection fraction (LVEF) decrease or definite or probable cardiac death; and incidence of LVSD, defined as an absolute decrease in LVEF of at least 10 percentage points below the baseline measurement and to below 50% by LVEF measurements over the course of the study.

All verbatim AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and AE severity will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), v4. Congestive heart failure, in addition, will be graded according to the New York Heart Association (NYHA) functional classification. All AEs, including SAEs, will be summarized by treatment arm and CTCAE grade. System Organ Class and Preferred Term will be presented. In addition, AEs leading to discontinuation of study treatment will be summarized by treatment arm. For each patient's AEs, the maximum severity recorded will be used in the summaries.

Laboratory toxicities will be defined based on local laboratory normal ranges and NCI-CTCAE, v4. Selected laboratory abnormalities such as worst toxicity grade and

toxicity grade shift from baseline will be summarized by treatment arm. Change from baseline in targeted vital signs and laboratory results will also be assessed.

Selected AEs of particular importance (see Section 5.3.4 in the protocol) will also be analyzed, similar to the method for AEs.

For this study the following will be used to characterize reactions related to the administration of study drug(s):

- Investigator-assessed Administration Related Reactions (ARRs), including:
  - Injection-site reactions (Local), defined as any local morphological or physiological change at or near the SC injection site
  - Injection-related reactions (Systemic), defined as any system reaction in response to the SC injection of study drug
  - Infusion-related reactions (Systemic), defined as any system reaction in response to the IV infusion of study drug

ARRs potentially associated with IV or SC administration of study drug(s), defined as AEs in the SMQ "Anaphylactic Reaction (wide)", Roche Standard AEGT "Anaphylaxis and Hypersensitivity" and "Infusion-Related Reactions and Hypersensitivity", or the dictionary-derived term "Cytokine Release Syndrome" occurring during infusion/injection or within 24 hours of the end of administration, should be assessed as to whether considered related or unrelated to study drug by the investigator (see Sections 5.1.1.1 and 5.2.5.2 in the protocol for additional information about ARRs).

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

Cardiac AEs will be categorized according to the following endpoint criteria:

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

- Secondary cardiac endpoints:
  - Incidence of an asymptomatic or mildly symptomatic LVSD ("Ejection fraction decreased") of NYHA Class II, defined as an LVEF decrease of ≥ 10%-points below the baseline measurement to an absolute LVEF value of < 50%, confirmed by a second assessment within approximately 3 weeks confirming a decrease of ≥ 10%-points below the baseline measurement and to an absolute LVEF value of < 50%.

Other cardiac events, such as acute coronary syndrome, acute myocardial infarction, severe rhythm disturbances requiring treatment, etc., will be reported.

The assessment of the cardiac endpoint will be based on data from randomization until the start of any new therapy for recurrence of disease.

4.6.1 Exposure of Study Medication

The number of patients who experience a dose delay, dose modification, dose discontinuation, and reasons for the study treatment discontinuation will be summarized by treatment arm. Descriptive statistics will be presented for number of cycles received, total cumulative dose, dose intensity, and weeks of exposure for chemotherapy, trastuzumab, and pertuzumab.

4.6.2 Adverse Events

Verbatim descriptions of treatment-emergent AEs will be mapped to MedDRA thesaurus terms and graded according to the NCI CTCAE v4. All AEs, including SAEs, will be summarized by treatment arm and NCI CTCAE grade. In addition, AEs leading to discontinuation of the study treatment will be summarized by treatment arm. The maximum severity recorded for each AE will be used in the summaries.

4.6.3 Laboratory Data

Clinical laboratory tests will be performed at local laboratories. Laboratory abnormalities will be defined based on local laboratory normal ranges and NCI CTCAE v4.0. Select laboratory abnormalities such as worst toxicity grade and toxicity grade shift from baseline will be summarized by treatment arm. Roche Standard Reference Ranges will be implemented before any data is summarized for reporting and analysis, and the lab standardization process will be detailed in the Data Analysis Plan (DAP) Module 2.

4.6.4 Vital Signs

Vital signs (including systolic and diastolic blood pressure, pulse rate, and body temperature) and physical measurements (including body weight and height) recorded before administration of the study treatment and recorded before and after HER2-directed therapy will be listed and summarized with changes from baseline. Vital signs collected at unscheduled visits will be excluded from the summary table. The mean, standard deviation, median, and minimum and maximum values will be presented by treatment arm.

4.7 MISSING DATA

Patients with missing PK data (such as Cycle 7 Ctrough) at time of the primary endpoint Cycle 7 Ctrough (pre-dose Cycle 8) will be excluded from the per protocol PK population.

Patients with missing data for tpCR (i.e., do not undergo surgery or have an invalid pCR assessment) will be included in the analysis and will be classed as non-responders.

For iDFS, iDFS including second primary non-breast cancer, EFS, EFS including secondary primary non-breast cancer, and OS data from all randomized patients will be analyzed. Data for patients who are randomized without any post-baseline assessments will be censored at the time of randomization plus 1 day. For iDFS, patients who do not undergo surgery will be excluded from the analysis. Patients without any post-surgery assessment will be censored at time of surgery plus 1 day. For OS, patients not experiencing an event will be censored at the date when they were last known to be alive and event-free.

Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, MULTICENTER, OPEN-LABEL, TWO-ARM STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**
PROTOCOL NUMBER:	WO40324
VERSION NUMBER:	2
EUDRACT NUMBER:	2017-004897-32
IND NUMBER:	131009
TEST PRODUCT:	Fixed-dose combination (FDC) of pertuzumab and trastuzumab for subcutaneous administration (RO7198574)
PHASE:	Phase III
INDICATION:	HER2-positive Early Breast Cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the pharmacokinetics, efficacy, and safety of the fixed-dose combination (FDC) of pertuzumab and trastuzumab for SC administration compared with the Perjeta IV and Herceptin IV formulations in patients with HER2-positive early $breast$ cancer (EBC).

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

Primary Objective	Corresponding Endpoint
• To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough} of pertuzumab SC within the FDC compared with Perjeta IV	• Serum pertuzumab C_{trough} during Cycle 7 (pre-dose Cycle 8)
Secondary Pharmacokinetic Objective	**Corresponding Endpoint**
• To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum trastuzumab C_{trough} of trastuzumab SC within the FDC compared with Herceptin IV	• Serum trastuzumab C_{trough} during Cycle 7 (pre-dose Cycle 8)

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of the SC FDC of pertuzumab and trastuzumab + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy	• tpCR, defined as eradication of invasive disease in the breast and axilla (i.e., ypT0/isypN0), according to local pathologist assessment • iDFS, defined as the time from the first date of no disease (i.e., the date of primary surgery) to the first occurrence of one of the following events: - Ipsilateral invasive breast tumor 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) 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 PD or relapse. • iDFS, including second primary non-breast cancer, defined in the same way as iDFS but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) • EFS, defined as the time from enrollment to the first occurrence of one of the following events: - Breast cancer progression (PD) - Breast cancer recurrence (as defined for iDFS endpoint) - Death from any cause 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 PD or relapse. • EFS, including second primary non-breast cancer is defined in the same way as EFS, but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) • DRFI, defined as the time between randomization and the date of distant breast cancer recurrence • OS, defined as the time from randomization to death from any cause

Secondary Safety Objective	Corresponding Endpoints

• To evaluate the safety of the SC FDC of pertuzumab and trastuzumab compared with Perjeta IV and Herceptin IV	• Incidence and severity of adverse events and SAEs, with severity determined according to NCI CTCAE v4
	• Laboratory test abnormalities according to NCI CTCAE v4
	<u>Primary cardiac endpoints</u>
	• Incidence of a symptomatic ejection fraction decrease ("Heart failure") of NYHA Class III or IV and a drop in LVEF of at least 10-percentage points from baseline and to below 50%
	• Cardiac death, defined as one of the following:
	  • Definite cardiac death, defined as death due to heart failure, myocardial infarction, or documented primary arrhythmia
	  • Probable cardiac death, defined as sudden unexpected death within 24 hours of a definite or probable cardiac event (e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia) without documented etiology
	<u>Secondary cardiac endpoint</u>
	• Incidence of an asymptomatic or mildly symptomatic left ventricular systolic dysfunction ("Ejection fraction decreased") of NYHA Class II, defined as an LVEF decrease of $\geq$10-percentage points below the baseline measurement to an absolute LVEF value of $<$50%, confirmed by a second assessment within approximately 3 weeks confirming a decrease of $\geq$10-percentage points below the baseline measurement and to an absolute LVEF value of $<$50%

Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the pharmacokinetics of pertuzumab and trastuzumab following administration of the SC FDC	• Serum pertuzumab concentrations or PK parameters • Serum trastuzumab concentrations or PK parameters
• To compare the pharmacokinetics (including PK parameters such as AUC and C_{max}) following administration of the SC FDC versus Perjeta IV and Herceptin IV (in combination with chemotherapy)	• Serum pertuzumab concentrations or PK parameters during Cycle 7 (pre-dose Cycle 8) • Serum trastuzumab concentrations or PK parameters during Cycle 7 (pre-dose Cycle 8)
• To assess the pertuzumab PK profile and observed C_{trough} at Cycle 7 (pre-dose Cycle 8) and Cycle 12 (post-surgery) following FDC administration	• Serum pertuzumab concentrations during Cycle 7 (pre-dose Cycle 8) and Cycle 12 (pre-dose Cycle 13)
• To compare the pertuzumab exposure in Cycle 1 between Perjeta IV 840 mg and FDC (pertuzumab SC 1200 mg)	• Serum pertuzumab concentrations during Cycle 5

Exploratory Pharmacokinetic Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate potential relationships between pertuzumab exposure and the efficacy and safety of the SC FDC via a pertuzumab exposure-response analysis	• Relationship between serum concentration or PK parameters for pertuzumab and efficacy endpoints • Relationship between serum concentration or PK parameters for pertuzumab and safety endpoints
• To assess the impact of a potential PK DDI between pertuzumab and trastuzumab following administration of the SC FDC	• Serum concentrations or PK parameters for pertuzumab given in combination with trastuzumab compared with pertuzumab given alone (based on historical data) • Serum concentrations or PK parameters for trastuzumab given in combination with pertuzumab compared with trastuzumab given alone (based on historical data)
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of the SC FDC of pertuzumab and trastuzumab + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy	• bpCR, defined as eradication of invasive disease in the breast (i.e., ypT0/is, ypNx) • GBG pCR, defined as eradication of invasive and in situ disease in the breast and invasive disease in axilla (i.e., ypT0 ypN0) • Clinical response, defined as CR, PR, SD, or PD, prior to surgery. Tumor response will be assessed prior to each new cycle of therapy by clinical examination, mammography, and/or other methods of evaluation as per routine clinical practice. Response will be assessed by the investigator as per routine clinical practice.
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to pertuzumab, trastuzumab, and rHuPH20 with the SC FDC compared with Perjeta IV and Herceptin IV	• Incidence of pertuzumab ADAs during the study relative to the prevalence of ADAs at baseline • Incidence of trastuzumab ADAs during the study relative to the prevalence of ADAs at baseline • Incidence of rHuPH20 ADAs during the study relative to the prevalence of ADAs at baseline
• To evaluate potential effects of ADAs	• Relationship between pertuzumab ADA status and efficacy, safety, or PK endpoints • Relationship between trastuzumab ADA status and efficacy, safety, or PK endpoints • Relationship between rHuPH20 ADA status and efficacy, safety, or PK endpoints

Exploratory Biomarker Objectives	Corresponding Endpoint
• To explore potential association of tissue-based biomarkers or biomarker profiles to pCR • To explore changes in biomarker levels or biomarker profiles pre- and post-treatment based on tumor tissue • To assess blood-based biomarkers at baseline and longitudinally to explore changes over time and potential relationship to pCR and long-term efficacy endpoints	• Presence or absence of biomarker(s) and/or biomarker profiles with respect to levels of certain biomarkers at specified timepoints and relation to efficacy endpoints

ADA = anti-drug antibody; bpCR = breast pathologic complete response; C_{trough} = steady-state concentration; DRFI=distant breast cancer recurrence; DDI = drug-drug interaction; EFS = event-free survival; FDC = fixed-dose combination; GBG = German Breast Group; GMR = geometric mean ratio; HCP = health care provider; iDFS = invasive disease-free survival; IV = intravenous; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events ;OS = overall survival; pCR = pathologic complete response; PD = progressive disease; PK = pharmacokinetic; PR = partial response; SC = subcutaneous; SD = stable disease; tpCR = total pathological complete response.

Study Design

Description of Study

This is a global Phase III, two-arm, open-label, multicenter, randomized study to investigate the pharmacokinetics, efficacy, and safety of the FDC (pertuzumab and trastuzumab for SC administration) in combination with chemotherapy in patients with HER2-positive EBC in the neoadjuvant/adjuvant setting.

The study will enroll patients with HER2-positive breast cancer consistent with the indication for treatment with neoadjuvant Perjeta and Herceptin and chemotherapy in routine clinical practice and as recommended in local guidelines.

Approximately 500 patients with HER2-positive, operable or locally advanced/inflammatory breast cancer with a tumor size of >2 cm or node-positive will be randomized to one of the following treatment arms in a 1:1 ratio:

- **Arm A** (Perjeta IV + Herceptin IV): Patients will receive 8 cycles of neoadjuvant chemotherapy. This will include 4 cycles of ddAC every 2 weeks (Q2W) (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel Q1W for 12 weeks or 4 cycles of doxorubicin plus cyclophosphamide (AC) Q3W followed by docetaxel Q3W for 4 cycles. Perjeta + Herceptin will be given IV for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, patients will undergo surgery. Thereafter, patients will receive an additional 14 cycles of Perjeta IV and Herceptin IV for a total of 18 cycles. One year of HER2-targeted therapy without any delays would encompass 18 cycles.

After surgery (from Cycle 9 onwards), patients in Arm A *will continue Perjeta IV and* are allowed to switch from Herceptin IV to Herceptin SC, at the discretion of the investigator, in the countries where Herceptin SC is routinely used.

- **Arm B** (FDC of pertuzumab and trastuzumab for SC administration): Patients will receive 8 cycles of neoadjuvant chemotherapy. This will include 4 cycles of ddAC Q2W (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel Q1W for 12 weeks or 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. FDC will be given SC for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, patients will undergo surgery. Thereafter, patients will receive an additional 14 cycles of the FDC for a total of 18 cycles. One year of HER2-targeted therapy without any delays would encompass 18 cycles.

The investigator will select one of the two protocol-approved neoadjuvant chemotherapy regimens with which to treat the patient. Once the investigator's choice of chemotherapy has been made and eligibility confirmed, the patient will be randomized to one of the two treatment arms using a permuted blocks randomization procedure and stratified according to the following factors:

- Hormonal receptor status (based on central assessment):
  - Estrogen receptor (ER)-positive or progesterone receptor (PgR)-positive
  - ER-negative and PgR-negative
- Clinical stage at presentation:
  - Stage II–IIIA
  - Stage IIIB–IIIC
- Type of chemotherapy:
  - ddAC followed by paclitaxel
  - AC followed by docetaxel

A patient may only be randomized once in this trial. Patients randomized into the study will not be replaced. Patients who choose to withdraw after screening, but before randomization, will be replaced.

Number of Patients

Approximately 500 patients with centrally confirmed HER2-positive, Stage II–IIIC breast cancer with a tumor size of >2 cm, or node-positive *disease* (clinically *or* on imaging and *node positivity confirmed with* cytology *and/or* histopathology) will be randomized in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- 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 (ECOG) Performance Status* ≤ 1
- Female and male patients with Stage II–IIIC (T2–T4 *plus any N, or any T plus N1–3*, M0), locally advanced, inflammatory, or early-stage, unilateral, and histologically confirmed invasive breast cancer

  Patients with inflammatory breast cancer must be able to have a core-needle biopsy
- Primary tumor >2 cm in diameter, or node-positive *disease* (clinically *or* on imaging, and *node positivity confirmed with* cytology *and/or* histopathology)
- HER2-positive breast cancer confirmed by a central laboratory prior to study enrollment. HER2-positive status will be determined based on pretreatment breast biopsy material and defined as 3+ by IHC and/or positive by *HER2* amplification by in situ hybridization (ISH) with a ratio of ≥ 2 for the number of *HER2* gene copies to the number of signals for chromosome 17 copies

  Patients with multifocal tumors (more than one tumor confined to the same quadrant as the primary tumor) are eligible provided at least one focus is sampled and centrally confirmed as HER2 positive.

- Hormone receptor status of the primary tumor, centrally confirmed

  Hormone receptor-positive status can be determined by either known ER-positive and/or known PgR-positive status. Hormone receptor-negative status must be determined by both known ER-negative and known PgR-negative status
- Patient agreement to undergo mastectomy or breast conserving surgery after neoadjuvant therapy
- Availability of formalin-fixed, paraffin-embedded (FFPE) tumor tissue block for central confirmation of HER2 and hormone receptor status and additional biomarker research (e.g., *PIK3CA* mutational analyses)
- Baseline LVEF $\geq$ 55% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
- For women of childbearing potential (WOCBP) who are sexually active: agreement to remain abstinent (refrain from heterosexual intercourse) or use one highly effective non-hormonal contraceptive method with a failure rate of $<$ 1% per year, or two effective non-hormonal contraceptive methods during the treatment period and for 7 months after the last dose of HER2-targeted therapy*, and agreement to refrain from donating eggs during this same period*

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of highly effective 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).

  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 postovulation methods) and withdrawal are not acceptable methods of contraception (see Section 5.1.3).
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom in combination with a spermicidal foam, gel, film, cream, or suppository, 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 with a spermicidal product during the treatment period and for 7 months after the last dose of HER2-targeted therapy 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 postovulation methods) and withdrawal are not acceptable methods of contraception (see section 5.1.3).
- A negative serum pregnancy test must be available prior to randomization for WOCBP (premenopausal women and women $<$ 12 months after the onset of menopause), unless they have undergone surgical sterilization (removal of ovaries and/or uterus)
- 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

Exclusion Criteria

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

- Stage IV (metastatic) breast cancer
- Patients with a history of invasive breast cancer

- Patients with a history of concurrent or previously treated non-breast malignancies except for appropriately treated 1) non-melanoma skin cancer and/or 2) in situ carcinomas, including cervix, colon, and skin

  A patient with previous invasive non-breast cancer is eligible provided he/she has been disease free for more than 5 years.
- Patients who have received any previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy (selective estrogen receptor modulators, aromatase inhibitors, and antitumor vaccines) for treatment or prevention of breast cancer, or radiation therapy for treatment of cancer
- Patients who have a past history of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) if they have received any systemic therapy for its treatment or radiation therapy to the ipsilateral breast

  Patients are allowed to enter the study if treated with surgery alone.
- Patients with high-risk for breast cancer who have received chemopreventative drugs in the past are not allowed to enter the study
- Patients with multicentric (multiple tumors involving more than one quadrant) breast cancer, unless all tumors are HER2-positive
- Patients with bilateral breast cancer
- Patients who have undergone an excisional biopsy of primary tumor and/or axillary lymph nodes
- Axillary lymph node dissection (ALND) prior to initiation of neoadjuvant therapy

  Patients with clinically negative axilla (by physical examination and radiographic imaging) may undergo a core or needle biopsy procedure prior to neoadjuvant systemic therapy if in keeping with local practice
- Sentinel lymph node biopsy (SLNB) prior to neoadjuvant therapy
- Treatment with any investigational drug within 28 days prior to randomization
- Serious cardiac illness or medical conditions including, but not confined to, the following:
  - History of NCI CTCAE (v4) Grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) Class $\geq$ 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 2] or third-degree AV-block)
  - Serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality
  - Angina pectoris requiring anti-anginal medication
  - Clinically significant valvular heart disease
  - Evidence of transmural infarction on ECG
  - Evidence of myocardial infarction within 12 months prior to randomization
  - Poorly controlled hypertension (e.g., systolic >180 mm Hg or diastolic >100 mmHg)
- Inadequate bone marrow function, defined as:
  - Absolute neutrophil count $< 1.5 \times 10^9$/L
  - Platelet count $< 100 \times 10^9$/L
  - Hemoglobin <9 g/dL
- Impaired liver function, defined as:
  - Serum (total) bilirubin $> 1.25 \times$ upper limit of normal (ULN)

    In case of Gilbert's syndrome: a total bilirubin of $2 \times$ ULN is permitted.
  - Aspartate aminotransferase (AST) and/*or* alanine aminotransferase (ALT) $> 1.25 \times$ ULN

- Albumin < 25 g/L

- Inadequate renal function with serum creatinine $> 1.5 \times$ 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 7 months after the last dose of HER2-targeted therapy

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- 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 HIV
- Known hypersensitivity to study drugs, excipients, and/or murine proteins
- Current chronic daily treatment with corticosteroids (dose > 10 mg methylprednisolone or equivalent excluding inhaled steroids)
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, *colon, skin, and/or* non-melanoma skin carcinoma
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe LVSD, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome

End of Study

The end of the study is expected to occur approximately 4.5 years after the last patient is randomized to the study. The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient (or when all patients have died or the trial is terminated by the Sponsor, whichever is earliest).

Length of Study

The total length of the study, from screening of the first patient to the end of the study is expected to be approximately 5.5 years.

Investigational Medicinal Products

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

Test Product (Investigational Drug)

For patients randomized to receive the FDC SC, the FDC is given as a fixed non–weight-based dose. A loading dose of 1200 mg SC pertuzumab and 600 mg SC trastuzumab is then followed by 600 mg SC pertuzumab and 600 mg SC trastuzumab Q3W. Chemotherapy should be given after the FDC.

After surgery, patients continue to receive the FDC in the adjuvant setting until a total of 18 cycles of the FDC have been administered during the study. Adjuvant FDC treatment should not start until at least 2 weeks after surgery. If the interval between the first dose of adjuvant FDC and the last dose of neoadjuvant FDC *is* ≥ 6 weeks, a reloading dose of FDC (1200 mg of pertuzumab and 600 mg of trastuzumab) is required. Subsequent maintenance FDC doses (600 mg pertuzumab and 600 mg trastuzumab) will then be given Q3W, starting 3 weeks later. The interval between the last dose of neoadjuvant FDC and the first dose of adjuvant FDC should be ≤ 9 weeks.

Comparator

For patients randomized to receive the IV formulations of Perjeta and Herceptin, Perjeta is given as a fixed non–weight-based dose of 840-mg IV loading dose and then 420-mg IV Q3W. Herceptin is given as an 8-mg/kg IV loading dose and then 6 mg/kg IV Q3W. The order of administration of Perjeta and Herceptin is according to investigator preference. Chemotherapy should be given after Perjeta and Herceptin.

After surgery, patients continue to receive Perjeta and Herceptin in the adjuvant setting until a total of 18 cycles of Perjeta and Herceptin have been administered during the study (neoadjuvant and adjuvant). Adjuvant Perjeta and Herceptin treatment should not start until 2 weeks after surgery. If the interval between the first dose of adjuvant Perjeta and Herceptin and the last dose of neoadjuvant Perjeta and Herceptin exceeds 6 weeks, a reloading dose of 840 mg of Perjeta and 8 mg/kg of Herceptin is required. The interval between the last dose of neoadjuvant Perjeta and Herceptin and the first dose of adjuvant Perjeta and Herceptin should be $\leq$9 weeks.

Non-Investigational Medicinal Products

Doxorubicin, cyclophosphamide, paclitaxel, docetaxel, G-CSF, and adjuvant hormone therapy are administered in accordance with local prescribing information and these drugs are not regarded as IMPs. These drugs will be obtained locally by the investigational sites or will be provided by the Sponsor as per country requirements.

Statistical Methods

Primary Analysis

The primary endpoint of this study is observed pertuzumab trough concentration (C_{trough}) at Cycle 7 (i.e., the measured pre-dose concentration value at Cycle 8), following 3 cycles of Perjeta IV and Herceptin IV or FDC (pertuzumab and trastuzumab SC). Pertuzumab C_{trough} will be analyzed at the time of the primary analysis, which will occur *after* the last *patient has completed (all)* neoadjuvant therapy and *has undergone* surgery.

The non-inferiority of the SC and IV dose of pertuzumab will be assessed by a one-sided testing procedure. The C_{trough}SC/C_{trough}IV GMR of the SC dose of pertuzumab relative to the IV dose will be estimated together with the two-sided 90% CI based on the log-transformed trough concentration values. The null hypothesis will be rejected and non-inferiority will be concluded if the lower bound of the 90% CI of the GMR is $\geq$0.8.

Determination of Sample Size

The study is designed to have at least 80% power to demonstrate non-inferiority of the Cycle 7 (i.e., pre-dose Cycle 8) pertuzumab serum C_{trough} from pertuzumab SC within FDC to the Perjeta IV formulation in patients with HER2-positive EBC.

The hypothesis to be tested for the primary endpoint, observed pertuzumab C_{trough}, is:

- H0: The SC dose is inferior to the IV dose (i.e., the C_{trough}SC/C_{trough}IV GMR of the SC dose of pertuzumab relative to the IV dose is not greater than 0.8) versus
- H1: The SC dose is non-inferior to the IV dose (i.e., C_{trough}SC/C_{trough}IV GMR of the SC dose of pertuzumab relative to the IV dose is equal to or greater than 0.8)

The null-hypothesis will be rejected if the lower bound of the 90% CI for the GMR is equal or greater than 0.8.

PK sample size calculations are based on the coefficient of variation (CV)% for the C_{trough} of trastuzumab observed from previous studies in MBC and EBC patients after Q3W treatment. With a CV of 60% assumed, a minimum or 130 patients per arm (i.e., a total of 260 patients) is needed to demonstrate C_{trough} non-inferiority with a power of 80% if the true means of the two formulations do not differ by more than 5%. An additional 240 patients will also be recruited to provide a substantial database to assess tpCR and safety profile comparability. Therefore, a total of approximately 500 patients (~250 patients per arm) will provide a sufficient sample size to test the primary PK hypothesis and also assess efficacy and safety profile comparability.

A hierarchical testing procedure for key secondary endpoints will be used to control the overall type I error rate at *a one-sided 5% significance level.*

Interim *And Final* Analyses

No formal, statistical interim analyses are planned prior to the primary analysis.

The final analysis will occur 3 years after the last patients last treatment.

Appendix 2 Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase

This study is driven by the primary endpoint C_{trough}. Therefore, adherence to the PK assessment schedule is of utmost importance.

	Screening	Baseline	Treatment Period														
			3-Week Cycles				3-Week Cycles										
Cycle			1	2	3	4	5			6	7					8	Surgery [a]
Day	–28 to –1	–7 to –1	1	1	1	1	1	2	15	1	1	2	4	8	15	1	1
Informed consent [b]	x																
Medical history and demographics	x																
Complete physical examination [c, d]	x		x													x	
Limited physical examination [d]				x	x	x	x			x	x						
Vital signs [e, d]	x		x	x	x	x	x			x	x					x	
ECOG Performance Status [c, d, f]		x	x [g]	x	x	x	x			x	x					x	
Height [d]	x																
Weight [c, d, h]	x		x	x	x	x	x			x	x					x	
Tumor staging [i]	x																
Bilateral mammogram (or another imaging method as per local practice) [j]	x															x	
Clinical tumor assessment/breast examination [d, k]	x		x	x	x	x	x			x	x					x	

Appendix 2 Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase (cont.)

	Screening	Baseline	Treatment Period														
			3-Week Cycles				3-Week Cycles										
Cycle			1	2	3	4	5			6	7					8	Surgery [a]
Day	–28 to –1	–7 to –1	1	1	1	1	1	2	15	1	1	2	4	8	15	1	1
ECG *(12-lead)*	x						x										
LVEF (ECHO or MUGA) [l]	x						x [m]				x						*x*
Hematology/Biochemistry [n]		x	x [g]	x	x	x	x			x	x					x	
Pregnancy test [o]		x				x					x						
FFPE tumor tissue sample for central HER2/HR testing and exploratory biomarker research [p]	x																
Local HER2 and hormone receptor status (HER2, ER, PgR) [q]	x																
Tumor sample [r]																	x
Pathologist post-surgery pathologic response tumor assessment [s]																	x
PK sampling: Pertuzumab/Trastuzumab IV (Arm A) [t]							x [u,v]	x	x	x [u,v]	x [u,v]	x	x	x	x	x [u,v]	

Appendix 2 Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase (cont.)

	Screening	Baseline	Treatment Period													
			3-Week Cycles				3-Week Cycles									
Cycle			1	2	3	4	5			6	7				8	Surgery [a]
Day	–28 to –1	–7 to –1	1	1	1	1	1	2	15	1	1	2	4	8	15	1	1
ADA sampling: Pertuzumab/Trastuzumab IV (Arm A)		x [w]								x [u]							
PK sampling: Pertuzumab/Trastuzumab SC (Arm B) [t]							x [x]	x	x	x [x]	x [x]	x	x	x	x	x [x]	
ADA sampling: Pertuzumab/Trastuzumab/ rHuPH20 SC (Arm B)		x [w]								x [x]							
Plasma sample for ctDNA *(biomarker)* [y]		x [w]														x	
Perjeta IV (Arm A) [z]							x			x	x					x	
Herceptin IV (Arm A) [z]							x			x	x					x	
FDC SC (Arm B) [aa]							x			x	x					x	
Doxorubicin [bb]			x	x	x	x											
Cyclophosphamide [bb]			x	x	x	x											
Docetaxel [cc]							x			x	x					x	

Appendix 2 Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase (cont.)

	Screening	Baseline	Treatment Period														
			3-Week Cycles				3-Week Cycles										
Cycle			1	2	3	4	5			6	7					8	Surgery [a]
Day	–28 to –1	–7 to –1	1	1	1	1	1	2	15	1	1	2	4	8	15	1	1
Adverse events [dd]			All AEs and SAEs (see Section 5.3)														
Concomitant medication [ee]		*x*	Continuous														

AC = doxorubicin and cyclophosphamide; ADA = anti-drug antibody; β-HCG = human chorionic gonadotripin; CBE = clinical breast examination; CT = computed tomography; ctDNA = circulating tumor DNA; Ctrough = steady-state concentration; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; FDC = fixed-dose combination of pertuzumab and trastuzumab for SC administration;
FFPE = formalin-fixed, paraffin-embedded; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquistion; NCCN = National Comprehensive Cancer Network; PgR = progesterone receptor; PK = pharmacokinetic; Q3W = every three weeks; RBR = Research Biosample Repository; rHuPH20 = recombinant human PH20 hyaluronidase; SAE = serious adverse event.
Notes: Cycle 1, Day 1 = first dose of study drug. *Patients should receive their first dose of study drug on the day of randomization, if possible. If this is not possible, the first dose should occur no later than 3 days after randomization. Clinical visits must be scheduled within ±3 days of the day specified.* On dosing days, PK samples need to be taken on the exact day of the visit schedule. On non-dosing days, PK samples must be taken within ± 2 days of the required sampling day, with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded).

[a] Surgery will be performed no earlier than 14 days following the last infusion or injection of neoadjuvant therapy. The interval between the last dose of neoadjuvant Perjeta and Herceptin IV or FDC and the first dose of adjuvant Perjeta and Herceptin IV or FDC should be ≤ 9 weeks.

[b] Results of standard-of-care tests or examinations performed prior to obtaining informed consent may be used; such tests do not need to be repeated for screening.

[c] Must be performed pre-dose on dosing days.

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

[e] Vital signs (respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature) will be taken before the administration of study treatment and before and after Perjeta and Herceptin infusions/FDC injections.

[f] ECOG Performance Status should be assessed when the patient undergoes clinical tumor assessment and breast examination (i.e., prior to

Appendix 2 Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase (cont.)

each new cycle of therapy during neoadjuvant treatment and at least every 3 months during the adjuvant treatment period [Cycle 9, Cycle 13, Cycle 17, and Cycle 21] and at the treatment completion or discontinuation visit).

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

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

[i] Baseline tumor staging procedures are not mandatory and should be performed as per local practice, in alignment with national guidelines and as clinically indicated within 28 days of randomization. See Section 4.5.7.2.

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

[k] Clinical breast examination (CBE) will be performed at screening. During the neoadjuvant treatment period, tumor response assessment will be performed prior to each new cycle of therapy by CBE (mandatory) and other methods of evaluation as per routine clinical practice.

[l] For patients whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each patient and is preferably performed and assessed by the same assessor. All LVEF assessments will be performed during Days 15 – 21 of three-week cycles prior to the cycle indicated here to allow evaluation of the results before the next treatment cycle. LVEF assessment may also be performed on Day 1 of treatment but results must be available before treatment is administered.

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

[n] Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Biochemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, albumin, ALP, ALT, AST, total bilirubin and direct/indirect bilirubin (if needed). Bilirubin fractions (direct and indirect) need to be measured only if total bilirubin is greater than ULN. Bicarbonate should only be tested at sites where this test is part of the standard safety laboratory panel. During the treatment period, bloods for hematology/biochemistry must be taken predose but may be taken within 3 days prior to treatment day.

[o] For all women of childbearing potential and for all women not meeting the definition of postmenopausal (refer to Section 5.1.3 for definition), pregnancy test must be performed via serum β-HCG at baseline within 7 days prior to the first administration of study medication (with result available prior to dosing). Urine pregnancy tests should be repeated during the treatment period within 7 days prior to every third treatment cycle starting at Cycle 4 (and as clinically indicated), as well as at the treatment discontinuation visit and every 3 months

Appendix 2 Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase (cont.)

thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. A pregnancy test at 7 months (i.e., between 6–9 months follow up) can be performed if indicated. Note that patients are required to continue contraception for 7 months after study treatment is complete.

[p] FFPE tumor tissue sample will be collected for mandatory central confirmation of HER2 and hormone receptor status. Additional mandatory exploratory biomarker analysis (such as PIK3CA), storage, and analysis, as part of the RBR (optional) only, apply for randomized patients. Retrieval, submission, and central testing of tumor tissue sample can occur outside the 28-day screening period.

[q] Hormone receptor–positive patients are to be prescribed endocrine therapy according to the guidelines after completion of pre-operative chemotherapy and surgery. Local HER2/HR assessment can occur outside the 28-day screening period.

[r] Optional submission of post-treatment samples obtained from resection specimens from all consenting patients for exploratory biomarkers.

[s] Pathological response assessment to be performed using the resected specimen by the local pathologist on the basis of guidelines to be provided in the Pathology Manual.

[t] The date and time of PK sampling must be carefully recorded in all cases. On dosing days, PK samples must be taken on the exact day when HER2-targeted therapy is administered (no window allowed). On non-dosing days, all samples must be taken on the exact day of the visit schedule whenever possible (± 2 days is allowed if necessary), with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded) [redacted]. If the Cycle 8 dose administration is going to be delayed by more than 2 days, the Cycle 8 pre-dose sample must be taken 21 days after Cycle 7 administration. This exception does not apply to any other cycles.

[u] Take sample pre-infusion.

[v] Take additional PK sample at the end of the infusion. The time of sampling must be within 15 minutes after each infusion has ended.

[w] Sample can be taken after randomization but prior to drug administration on Cycle 1, Day 1.

[x] Take sample pre-injection.

[y] Mandatory plasma samples collected at baseline, at Cycles 8 and 10, the treatment completion or treatment discontinuation visit and at 3-year follow up.

[z] All patients in Arm A receive a Perjeta loading dose of 840 mg IV on Cycle 5, Day 1 (the first day of paclitaxel treatment). Thereafter (Cycles 6 – 22), all patients receive a Perjeta maintenance dose of 420 mg IV. All patients in Arm A receive a Herceptin loading dose of 8 mg/kg IV on Cycle 5, Day 1 (the first day of paclitaxel treatment). Thereafter (Cycles 6 – 22), all patients receive Herceptin at 6 mg/kg IV. The order of administration of Perjeta and Herceptin is according to the investigator's preference.

Appendix 2 Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase (cont.)

[aa] All patients in Arm B receive a FDC SC loading dose of 1200mg pertuzumab and 600mg trastuzumab on Cycle 5, Day 1 (the first day of paclitaxel treatment). Thereafter (Cycles 6 – 22), all patients receive maintenance dose of 600mg pertuzumab and 600mg trastuzumab.

[bb] All patients receive doxorubicin 60 mg/m2 IV and cyclophosphamide 600 mg/m2 IV given every 3 weeks, for four cycles (Cycles 1 – 4), according to local practice guidelines.

[cc] The starting dose of docetaxel is 75mg/m2 IV in Cycle 5 given every 3 weeks. At the investigator's discretion, the dose may be escalated to 100 mg/m2 IV for subsequent cycles (Cycles 6 – 8) provided no dose-limiting toxicity occurs.

[dd] After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by protocol-mandated intervention should be reported. After initiation of study drugs, all adverse events and serious adverse events will be collected until the treatment completion or discontinuation visit (28 days after the last dose of study drug). Non-serious adverse events occurring prior to study drug administration (Cycle 1, Day 1) will be reported in the medical history unless adverse event reporting is deemed more appropriate. After the treatment completion or discontinuation visit, drug-related serious adverse events and adverse events and serious adverse events that qualify for long-term reporting will continue to be collected (see Sections 5.3.4 and 5.5.2).

[ee] Concomitant medications will be recorded until the end of the treatment period.

Appendix 3 Schedule of Activities for Patients Receiving ddAC Q2W→Paclitaxel in the Neoadjuvant Phase

This study is driven by the primary endpoint C_{trough}. Therefore, adherence to the PK assessment schedule is of utmost importance.

	Screening	Baseline	Treatment Period														
			2-Week Cycles				3-Week Cycles										
Cycle			1	2	3	4	5			6	7					8	Surgery [a]
Day	–28 to –1	–7 to –1	1	1	1	1	1	2	15	1	1	2	4	8	15	1	1
Informed consent [b]	x																
Medical history and demographics	x																
Complete physical examination [c, d]	x		x													x	
Limited physical examination [c, d]				x	x	x	x			x	x						
Vital signs [d, e]	x		x	x	x	x	x			x	x					x	
ECOG Performance Status [c, d, f]		x	x [g]	x	x	x	x			x	x					x	
Height [d]	x																
Weight [c, d, h]	x		x	x	x	x	x			x	x					x	
Tumor staging [i]	x																
Bilateral mammogram (or another imaging method as, per local practice) [j]	x															x	
Clinical tumor assessment/breast examination [d, k]	x		x	x	x	x	x			x	x					x	

	Screening	Baseline	Treatment Period														
			2-Week Cycles				3-Week Cycles										
Cycle			1	2	3	4	5			6	7					8	Surgery [a]
Day	–28 to –1	–7 to –1	1	1	1	1	1	2	15	1	1	2	4	8	15	1	1
ECG *(12-lead)*	x						x										
LVEF (ECHO or MUGA) [l]	x						x [m]				x						*x*
Hematology/Biochemistry [n]		x	x [g]	x	x	x	x			x	x					x	
Pregnancy test [o]		x				x					x						
FFPE tumor tissue sample for central HER2/HR testing and exploratory biomarker research [p]	x																
Local HER2 and hormone receptor status (HER2, ER, PgR) [q]	x																
Tumor sample [r]																	x
Pathologist post-surgery pathologic response tumor assessment [s]																	x
PK sampling: Pertuzumab/Trastuzumab IV (Arm A) [t]							x [u,v]	x	x	x [u,v]	x [u,v]	x	x	x	x	x [u,v]	
ADA sampling: Pertuzumab/Trastuzumab IV (Arm A)		*x* [w]								x [u]							
PK sampling: Pertuzumab/Trastuzumab SC (Arm B) [t]							x [x]	x	x	x [x]	x [x]	x	x	x	x	x [x]	

	Screening	Baseline	Treatment Period													
			2-Week Cycles				3-Week Cycles									
Cycle			1	2	3	4	5			6	7				8	Surgery [a]
Day	–28 to –1	–7 to –1	1	1	1	1	1	2	15	1	1	2	4	8	15	1	1
ADA sampling: Pertuzumab/Trastuzumab/ rHuPH20 SC (Arm B)		x [w]								x [x]							
Plasma sample for ctDNA (biomarker) [y]		x [w]														x	
Perjeta IV (Arm A) [z]							x			x	x					x	
Herceptin IV (Arm A) [z]							x			x	x					x	
FDC SC (Arm B) [aa]							x			x	x					x	
ddDoxorubicin [bb]			x	x	x	x											
ddCyclophosphamide [bb]			x	x	x	x											
Paclitaxel [cc]							Weekly for 12 weeks										
Adverse events [dd]			All AEs and SAEs (see Protocol Section 5.3)														
Concomitant medication [ee]		x	Continuous														

ADA = anti-drug antibody; AE = adverse event; β-HCG = human chorionic gonadotripin; *CBE = clinical breast examination;* CT = computed tomography; ctDNA = circulating tumor DNA; C_{trough} = steady-state concentration; ddAC = dose-dense doxorubicin and cyclophosphamide; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; FDC = fixed-dose combination of pertuzumab and trastuzumab for SC administration; FFPE = formalin-fixed, paraffin-embedded; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquistion; NCCN = National Comprehensive Cancer Network; PgR = progesterone receptor; PK = pharmacokinetic; Q2W = every 2 weeks; RBR = Research Biosample Repository; rHuPH20 = recombinant human PH20 hyaluronidase; SAE = serious adverse event.

Notes: Cycle 1, Day 1 = first dose of study drug. *Patients should receive their first dose of study drug on the day of randomization, if possible. If this is not possible, the first dose should occur no later than 3 days after randomization.* Clinical visits must be scheduled within ±3 days of the day specified. On dosing days, PK samples need to be taken on the exact day of the visit schedule. On non-dosing days, PK samples must be taken within ±2 days of the required sampling day, with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded).

[a] Surgery will be performed no earlier than 14 days following the last infusion or injection of neoadjuvant therapy. The interval between the last dose of neoadjuvant Perjeta and Herceptin IV or FDC and the first dose of adjuvant Perjeta and Herceptin IV or FDC should be ≤9 weeks.

[b] Results of standard-of-care tests or examinations performed prior to obtaining informed consent may be used; such tests do not need to be repeated for screening.

[c] Must be performed pre-dose on dosing days.

[d] *Assessment may be done within 3 days prior to treatment day.*

[e] Vital signs (respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature) will be taken before the administration of study treatment and before and after Perjeta and Herceptin infusions/FDC injections.

[f] ECOG Performance Status should be assessed when the patient undergoes clinical tumor assessment and breast examination (i.e., prior to each new cycle of therapy during neoadjuvant treatment and at least every 3 months during the adjuvant treatment period [Cycle 9, Cycle 13, Cycle 17, and Cycle 21] and at the treatment completion or discontinuation visit).

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

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

[i] Baseline tumor staging procedures *are not mandatory and* should be performed *as per local practice,* in alignment with national guidelines *and as clinically indicated* within 28 days of randomization (see Protocol Section 4.5.7.2).

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

[k] Clinical *breast examination (CBE) will be performed at screening. During the neoadjuvant treatment period,* tumor *response* assessment will be performed *prior to each new cycle of therapy by CBE (mandatory) and other methods of evaluation* as per routine clinical practice.

[l] For patients whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each patient and is preferably performed and assessed by the same assessor. All LVEF assessments will be performed during Days 15 – 21 of 3-week cycles prior to the cycle indicated to allow evaluation of the results before the next treatment cycle. LVEF assessment may also be performed on Day 1 of treatment but results must be available before treatment is administered.

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

[n] Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Biochemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, albumin, *ALP,* ALT, AST, total bilirubin and direct/indirect bilirubin (if needed). Bilirubin fractions (direct and indirect) need to be measured only if total bilirubin is greater than ULN. Bicarbonate should only be tested at sites where this test is part of the standard safety laboratory panel. During the treatment period, bloods for hematology/biochemistry *must be taken predose but* may be taken within 3 days prior to treatment day.

[o] For all women of childbearing potential and for all women not meeting the definition of postmenopausal (refer to Section 5.1.3 for definition), pregnancy tests must be performed via serum β-HCG at baseline within 7 days prior to the first administration of study medication (with result available prior to dosing). Urine pregnancy tests should be repeated during the treatment period within 7 days prior to every third treatment cycle starting at Cycle 4 (and as clinically indicated), as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. *A pregnancy test at 7 months (i.e. between 6-9 month follow up) can be performed if indicated. Note that patients are required to continue contraception for 7 months after study treatment is complete.*

[p] FFPE tumor tissue sample will be collected for mandatory central confirmation of HER2 and hormone receptor status. *Additional mandatory exploratory biomarker analysis (such as PIK3CA), storage, and analysis, as part of the RBR (optional) only, apply for randomized patients. Retrieval, submission, and central testing of tumor tissue sample can occur outside the 28-day screening period.*

[q] Hormone receptor–positive patients are to be prescribed endocrine therapy according to the guidelines after completion of pre-operative chemotherapy and surgery. *Local HER2/HR assessment can occur outside the 28-day screening period.*

[r] Optional submission of post-treatment samples obtained from resection specimens from all *consenting* patients for exploratory biomarkers.

[s] Pathological response assessment to be performed using the resected specimen by the local pathologist on the basis of guidelines to be provided in a Pathology Manual.

[t] The date/time of PK sampling must be carefully recorded in all cases. *On dosing days, PK samples must be taken on the exact day when HER2-targeted therapy is administered (no window allowed). On non-dosing days, all samples must be taken on the exact day of the visit schedule whenever possible (±2 days is allowed if necessary*, with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded) [redacted]. *If the Cycle 8 dose administration is going to be delayed by more than 2 days, the Cycle 8 pre-dose sample must be taken 21 days after Cycle 7 administration. This exception does not apply to any other cycles.*

[u] Take sample pre-infusion.

[v] Take additional PK sample at the end of the infusion. The time of sampling must be within 15 minutes after *each* infusion has ended.

[w] *Sample can be taken after randomization but prior to drug administration on Cycle 1, Day 1.*

[x] Take sample pre-injection.

[y] Mandatory plasma samples collected at baseline, at Cycles 8 and 10, the treatment completion or treatment discontinuation visit and at 3-year follow up.

[z] All patients in Arm A receive a Perjeta loading dose of 840 mg IV on Cycle 5, Day 1 (the first day of paclitaxel treatment). Thereafter (Cycles 6 – 22), all patients receive a Perjeta maintenance dose of 420 mg IV. All patients in Arm A receive a Herceptin loading dose of 8 mg/kg IV on Cycle 5, Day 1 (the first day of paclitaxel treatment). Thereafter (Cycles 6 – 22), all patients receive Herceptin at 6 mg/kg IV. The order of administration of Perjeta and Herceptin is according to the investigator's preference.

[aa] All patients in Arm B receive a FDC SC loading dose of 1200mg pertuzumab and 600mg trastuzumab on Cycle 5, Day 1 (the first day of paclitaxel treatment). Thereafter (Cycles 6 – 22), all patients receive maintenance dose of 600mg pertuzumab and 600mg trastuzumab.

[bb] All patients receive doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV given every 2 weeks, for four cycles (Cycles 1 – 4), according to local practice guidelines.

[cc] All patients receive paclitaxel 80 mg/m^2 IV weekly for 12 weeks starting no sooner than 2 weeks after the last dose of doxorubicin and cyclophosphamide.

[dd] After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by protocol-mandated intervention should be reported. After initiation of study drugs, all adverse events and serious adverse events will be collected until the treatment completion or discontinuation visit (28 days after the last dose of study drug). Non-serious adverse events occurring prior to study drug administration (Cycle 1, Day 1) will be reported in the medical history unless adverse event reporting is deemed more appropriate. After the treatment completion or discontinuation visit, drug-related serious adverse events and adverse events and serious adverse events that qualify for long-term reporting will continue to be collected (see sections 5.3.4 and 5.5.2).

[ee] Concomitant medications will be recorded until the end of the treatment period.

Appendix 4 Schedule of Activities for All Patients in the Adjuvant Pertuzumab and Trastuzumab Treatment Phase

This study is driven by the primary endpoint C_{trough}. Therefore, adherence to the PK assessment schedule is of utmost importance.

Cycle (3 weeks)	9	10	11	12					13	14	15	16	17	18	19	20	21	22	Treatment Completion/ Discontinuation [a]
Day	1	1	1	1	2	4	8	15	1	1	1	1	1	1	1	1	1	1	
Complete physical examination																			x
Limited physical examination [b]	x	x	x	x					x	x	x	x	x	x	x	x	x	x	
Vital signs [b]	x	x	x	x					x	x	x	x	x	x	x	x	x	x	x
ECOG Performance Status [b, c]	x								x				x				x		x
Weight [b, d]	x	x	x	x					x	x	x	x	x	x	x	x	x	x	x
Bilateral mammogram (or another imaging method as, per local practice) [e]																			x
Clinical breast examination [b, f]	x								x				x				x		x
LVEF (ECHO or MUGA) [g]	x			x							x			x			x		x
Hematology/Limited Biochemistry [h]	x	x	x	x					x	x	x	x	x	x	x	x	x	x	
Pregnancy test [i]		x							x			x			x			x	x
Perjeta IV (Arm A) [j]	x	x	x	x					x	x	x	x	x	x	x	x	x	x	
Herceptin IV (Arm A) [j]	x	x	x	x					x	x	x	x	x	x	x	x	x	x	
FDC SC (Arm B) [k]	x	x	x	x					x	x	x	x	x	x	x	x	x	x	
PK sampling: Pertuzumab/Trastuzumab IV (Arm A) [l]	x [m,n]	x [m,n]	x [m,n]	x [m,n]	x	x	x	x	x [m]					x [m]				x [m]	

Appendix 4 Schedule of Activities for All Patients in the Adjuvant Pertuzumab and Trastuzumab Treatment Phase (cont.)

Cycle (3 weeks)	9	10	11	12					13	14	15	16	17	18	19	20	21	22	Treatment Completion/ Discontinuation [a]
Day	1	1	1	1	2	4	8	15	1	1	1	1	1	1	1	1	1	1	
ADA sampling: Pertuzumab/Trastuzumab IV (Arm A)	x [m]								x [m]					x [m]				x [m]	
PK sampling: Pertuzumab/Trastuzumab SC (Arm B) [l]	x [o]	x [o]	x [o]	x [o]	x	x	x	x	x [o]					x [o]				x [o]	
ADA sampling: Pertuzumab/Trastuzumab/ rHuPH20 SC (Arm B)	x [o]								x [o]					x [o]				x [o]	
Plasma sample for ctDNA (biomarker)		x																	x
Adverse events	All AEs and SAEs (see Section 5.3)																		
Concomitant medication	Continuous																		

Appendix 4 Schedule of Activities for All Patients in the Adjuvant Pertuzumab and Trastuzumab Treatment Phase (cont.)

ADA = anti-drug antibody; AE = adverse event; β-HCG = human chorionic gonadotripin; CT = computed tomography; ctDNA = circulating tumor DNA; C_{trough} = steady-state concentration; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FDC = fixed-dose combination of pertuzumab and trastuzumab for SC administration; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquistion; PK = pharmacokinetic; rHuPH20 = recombinant human PH20 hyaluronidase; SAE = serious adverse event; ULN = upper limit of normal.

Notes: Cycle 1, Day 1 = first dose of study drug. Clinical visits must be scheduled within ±3 days of the day specified. On dosing days, PK samples need to be taken on the exact day of the visit schedule. On non-dosing days, PK samples must be taken within ±2 days of the required sampling day, with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded).

[a] Treatment completion or discontinuation visits will optimally be scheduled for 28 (±3 days) following the last dose of study medication and will include all evaluations scheduled for the final visit.

[b] *Assessment may be done within 3 days prior to treatment day.*

[c] ECOG Performance Status should be assessed when the patient undergoes clinical tumor assessment and breast examination (i.e., at least very 3 months during the adjuvant treatment period [Cycle 9, Cycle 13, Cycle 17, and Cycle 21] and at the treatment completion or discontinuation visit).

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

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

[f] During the adjuvant treatment period, clinical breast examination should be performed to detect signs of locoregional relapse at least every 3 months (Cycle 13, Cycle 17, and Cycle 21) and at the treatment completion or discontinuation visit.

[g] For patients whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each patient and is preferably performed and assessed by the same assessor. All LVEF assessments will be performed during Days 15–21 of 3-week cycles prior to the cycle indicated here to allow evaluation of the results before the next treatment cycle. LVEF assessment may be performed on Day 1 of treatment but results must be available before treatment is administered.

[h] Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: *creatinine, alkaline phosphatase (ALP),* AST, ALT, total bilirubin, and direct/indirect bilirubin (if needed). Bilirubin fractions (direct and indirect) need to be measured only if total bilirubin is greater than ULN. During the treatment period, bloods for hematology/biochemistry *must be taken pre dose, but* may be taken within 3 days prior to treatment

day.

[i] For all women of childbearing potential and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea) who have not undergone surgical sterilization, pregnancy tests must be performed via serum β-HCG at baseline within 7 days prior to the first administration of study medication (with result available prior to dosing). Urine pregnancy tests should be repeated during the treatment period within 7 days prior to every third treatment cycle starting at Cycle 4 (and as clinically indicated), as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. *Pregnancy test at 7 months (i.e., between 6–9 month follow-up) can be performed if indicated. Note that patients are required to continue contraception for 7 months after study treatment is complete.*

[j] All patients receive a Perjeta maintenance dose of 420 mg IV. All patients receive Herceptin at 6 mg/kg IV. The order of administration of Perjeta and Herceptin is according to investigator preference. After surgery (from Cycle 9 onwards), patients in Arm A are allowed to switch from Herceptin IV to Herceptin SC, at the discretion of the investigator, in the countries where Herceptin SC is routinely used.

[k] All patients receive maintenance dose of 600 mg SC pertuzumab and 600 mg SC trastuzumab.The date and time of PK sampling must be carefully recorded in all cases. *On dosing days, PK samples must be taken on the exact day when HER2-targeted therapy is administered (no window allowed). On non-dosing days, all samples must be taken on the exact day of the visit schedule whenever possible (±2 days is allowed if necessary)* with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded).

[l] The date and time of PK sampling must be carefully recorded in all cases. *On dosing days, PK samples must be taken on the exact day when HER2-targeted therapy is administered (no window allowed). On non-dosing days, all samples must be taken on the exact day of the visit schedule whenever possible (±2 days is allowed if necessary)* with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded).

[m] Take sample pre-infusion.

[n] Take additional PK sample at the end of the infusion. The time of sampling must be within 15 minutes after *each* infusion has ended.

[o] Take sample pre-injection.

Appendix 5 Schedule of Activities for All Patients in the Treatment-Free Follow-Up

	Follow-up Visits [a]								
Month from the last dose of study drug	3	6	9	12	18	24	30	36	Every 6 months until end of study
Limited physical examination [b]	x	x	x	x	x	x	x	x	x
Vital signs [b]	x	x	x	x	x	x	x	x	x
ECOG Performance Status [b]	x	x	x	x	x	x	x	x	x
Assessment for recurrence [c]	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Clinical breast examination	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Bilateral mammogram				x		x		x	
Hematology/Limited Biochemistry [d]	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
LVEF (ECHO or MUGA) [e]		x		x	x	x		x	
Pregnancy test [f]	x	x							
PK sampling: Pertuzumab/Trastuzumab IV (Arm A) [g]	x	x							
ADA sampling: Pertuzumab/Trastuzumab IV (Arm A)	x	x		x	x	x	x	x	
PK sampling: Pertuzumab/Trastuzumab SC (Arm B) [g]	x	x							
ADA sampling: Pertuzumab/Trastuzumab/rHuPH20 SC (Arm B)	x	x		x	x	x	x	x	
Plasma samples for ctDNA (biomarker)								x	
Survival	x	x	x	x	x	x	x	x	x
Adverse events	AEs and SAEs are continuously monitored (see Section 5.4.1).								

Appendix 5 Schedule of Activities for All Patients in the Treatment-Free Follow-Up (cont.)

ADA = anti-drug antibody; AE = adverse event; β-HCG = human chorionic gonadotripin; ctDNA = circulating tumor DNA; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquistion; PK = pharmacokinetic; rHuPH20 = recombinant human PH20 hyaluronidase; SAE = serious adverse event.

Notes: Parentheses (x) indicate that the item is optional and required only if symptoms or clinical suspicion are present.

[a] Visit to be performed within ±15 days. These visits are based on time from last dose of study drug and not time from treatment completion/discontinuation visit, (i.e., 3-Month Follow-Up Visit is 3 months after last dose of study drug). After recurrence, all patients should continue to follow Appendix 4 for survival, LVEF assessments and pregnancy tests (pregnancies should be reported until 7 months after the last dose of study treatment, irrespective of disease progression or relapse or the initiation of alternative treatment). Related serious adverse events and non-breast second primary malignancies (reportable as serious adverse events) should also be reported until the end of the study.

[b] To be followed up *every* 3 *months* for 1 year, then *every* 6 *months* for an additional 2 years, then according to routine practice. After disease progression or relapse, patients need to only be followed for survival (i.e., physical examination, vital signs, and Performance Status do not need to be assessed).

[c] Assessment of distant disease recurrence to be performed if clinically indicated to exclude metastatic disease and within a timelines as per current standard of practice (see Section 4.5.12)

[d] Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: *creatinine, ALP,* AST, ALT, total bilirubin, and direct/indirect bilirubin (if needed). Bilirubin fractions (direct and indirect) need to be measured only if total bilirubin is greater than ULN

[e] After completion of HER2-directed therapy, LVEF is to be performed every 6 months for 2 years, then again 1 year later. For patients who discontinue HER2-directed therapy early for disease progression/relapse or due to adverse events (other than heart failure or LVEF decline), LVEF assessments should be performed every 6 months for 2 years, then annually for an additional year or until the initiation of alternative systemic therapy. For patients who discontinue HER2-directed therapy for heart failure or LVEF decline, LVEF assessments should be continued regardless of initiation of alternative systemic anti-cancer therapy until resolution, improvement to baseline status, no further improvement can be expected, or death. Additional LVEF assessments may be required for these patients (beyond those specified in the table) according to the investigator's clinical judgment. The results of these assessments should be reported.

[f] At 3 and 6 months after the last dose of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. *Pregnancy test at 7 months (i.e., between 6–9 month follow up) can be performed if indicated. Note that patients are required to continue contraception for 7 months after study treatment is complete.*

Appendix 5 Schedule of Activities for All Patients in the Treatment-Free Follow-Up (cont.)

[g] The date and time of PK sampling must be carefully recorded in all cases. *During follow-up*, samples must be taken ± 7 days of the required sampling day, with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]