STATISTICAL ANALYSIS PLAN

STUDY 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 CHINESE PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**

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STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AC	doxorubicin plus cyclophosphamide
ADA	anti-drug antibody
AE	adverse event
ARR	administration-related reaction
AUC	area under the concentration–time curve
bpCR	breast pathologic complete response
CI	Confidence interval
C_{max}	maximum serum concentration
C_{trough}	steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration)
CV	coefficient of variation
DRFI	distant recurrence-free inverval
EBC	early breast cancer
EFS	event-free survival
ER	estrogen receptor
FDC	fixed dose combination
GMR	geometric mean ratio
HER2	human epidermal growth factor receptor 2
HGRAC	Human Genetics Resources Administration of China
iDFS	invasive disease-free survival
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OS	overall survival
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetics
rHuPH20	recombinant human PH20 hylauronidase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous

Abbreviation or Term	Description
tpCR	total pathological complete response
TTE	time-to-event

1. INTRODUCTION

Study YO41137 is a Phase III, two-arm, open-label, multicenter, randomized study to investigate the pharmacokinetics (PK), efficacy, and safety of the fixed dose combination (FDC)(pertuzumab and trastuzumab for subcutaneous (SC) administration) in combination with chemotherapy in Chinese patients with human epidermal growth factor receptor 2-positive early breast cancer (HER2-positive EBC) in the neoadjuvant/adjuvant setting.

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

1.1 OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, efficacy, and safety of the FDC of pertuzumab and trastuzumab for SC administration compared with the Perjeta intravenous (IV) and Herceptin IV formulations in Chinese patients with HER2-positive EBC. Specific objectives and corresponding endpoints for the study are outlined below in Table 1.

Table 1 Study Objectives and Endpoints

Co-Primary Objectives	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)
• 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)

Table 1 Study Objectives and Endpoints (cont.)

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/is, ypN0), 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

Table 1 Study Objectives and Endpoints (cont.)

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 (cont.)**
• 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 trastuzumab and pertuzumab PK profile and observed C_{trough} at Cycle 7 (pre-dose Cycle 8)	• Serum pertuzumab concentrations during Cycle 7 (pre-dose Cycle 8) • Serum trastuzumab concentrations during Cycle 7 (pre-dose Cycle 8)
• To compare the pertuzumab exposure in Cycle 5 between Perjeta IV 840 mg and FDC (pertuzumab SC 1200 mg)	• Serum pertuzumab concentrations during Cycle 5

Table 1 Study Objectives and Endpoints (cont.)

• To evaluate potential relationships between pertuzumab and/or trastuzumab exposure and the efficacy and safety of the SC FDC via a pertuzumab and/or trastuzumab exposure-response analysis	• Relationship between serum concentration or PK parameters for pertuzumab and/or trastuzumab and efficacy endpoints • Relationship between serum concentration or PK parameters for pertuzumab and/or trastuzumab 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) • 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

Table 1 Study Objectives and Endpoints (cont.)

Exploratory Biomarker Objectives	Corresponding Endpoint
• To explore potential association of tissue-based biomarkers or biomarker profiles to pCR • 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 and relation to efficacy endpoints

ADA = anti-drug antibody; AUC = area under curve; bpCR = breast pathologic complete response; CR = complete response; C_{max} = maximum concentration; CR = complete response; C_{trough} = steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration); DRFI=distant breast cancer recurrence; DDI = drug-drug interaction; EFS = event-free survival; FDC = fixed-dose combination; 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 ;NYHA = New York Hear Association; OS = overall survival; pCR = pathologic complete response; PD = progressive disease; PK = pharmacokinetics; PR = partial response; SAE = serious adverse events; SC = subcutaneous; SD = stable disease; tpCR = total pathological complete response.

1.2 STUDY DESIGN

This is a Phase III, two-arm, open-label, multicenter, randomized study to investigate the PK, efficacy, and safety of the FDC (pertuzumab and trastuzumab for SC administration) in combination with chemotherapy in Chinese 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 200 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-4 cycles of doxorubicin plus cyclophosphamide (AC) every 3 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.
- Arm B (FDC of pertuzumab and trastuzumab for SC administration): Patients will receive 8 cycles of neoadjuvant chemotherapy: 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.

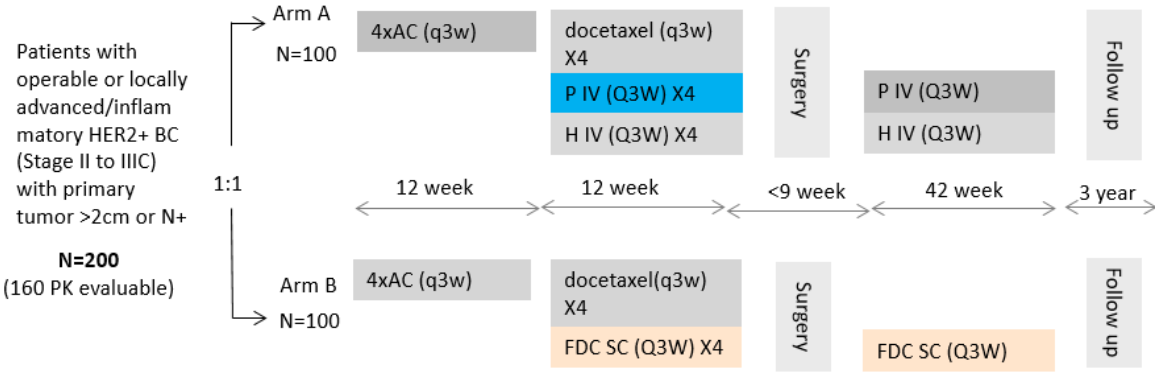
Once eligibility is confirmed, the patient will be randomized to one of the two treatment arms using a permuted blocks randomization procedure and stratified according to the following factors:

- 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

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.

Figure 1 presents an overview of the study design. The schedules of activities are provided in Appendix 1, Appendix 2, and Appendix 3 of the study protocol.

Figure 1 Study Schema



AC = doxorubicin plus cyclophosphamide; BC = breast cancer; FDC = fixed-dose combination of pertuzumab and trastuzumab SC; H = Herceptin; HER2 = human epidermal growth factor receptor 2; IV == intravenous; N += node positive; P = Perjeta; QW = once a week; Q3W = every 3 weeks; SC= subcutaneous.

Note: For Arms A and B, the doses of AC are doxorubicin 60 mg/m2 IV and cyclophosphamide 600 mg/m2 IV (AC is given Q3W). The starting dose of docetaxel is 75 mg/m2 IV in Cycle 5 (the first docetaxel cycle) and then 100 mg/m2 IV at the discretion of the investigator for Cycles 6-8, if no dose-limiting toxicity occurs (given Q3W). The 9-week period between neoadjuvant treatment and adjuvant treatment begins when the final dose of neoadjuvant treatment is administered.

Post-operative radiotherapy will be administered as per local practice, without interruption of the HER2-targeted therapy. Hormone receptor-positive patients should receive adjuvant hormonal treatment as per local practice.

1.2.1 Treatment Assignment and Blinding

This is an open-label study with approximately 200 Chinese patients randomized to two treatment arms in approximately 18 sites.

The investigator will use the protocol-approved neoadjuvant chemotherapy regimens with which to treat the patient.

Using an interactive voice or web-based response system (IxRS), patients will be randomized in a 1:1 ratio 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):
  - ER-positive or PgR-positive
  - ER-negative and PgR-negative
- Clinical stage at presentation
  - Stage II–IIIA
  - Stage IIIB–IIIC

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. Data for safety purposes will not be reviewed at an aggregate level prior to the primary analysis by the Study Management Team.

1.2.2 Analysis Timing

The primary analysis for PK will occur after the last patient has completed (all) neoadjuvant therapy and has undergone surgery. At this timepoint, secondary endpoints of total pathological complete response (tpCR) (and the exploratory pCR), clinical response, exploratory PK endpoints (as available), safety, immunogenicity and biomarkers (as available) will also be analyzed

The final analysis will occur 3 years after the last patient's last treatment. 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 and Immunogenicity (those not performed at the primary analysis) may also be assessed.

2. STATISTICAL HYPOTHESES

The following hypotheses will be tested on the co-primary PK endpoints:

- H0: The SC dose is inferior to the IV dose (i.e., the steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration) [C_{trough}] SC/C_{trough}IV geometric mean ratio (GMR) of the SC dose 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., the C_{trough}SC/C_{trough}IV GMR of the SC dose relative to the IV dose is equal or greater than 0.8)

The hierarchical testing procedure will follow the steps below:

1. Test the 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 Cycle 7 trastuzumab serum C_{trough}SC/C_{trough}IV, at a one-sided 5% significance level.

3. SAMPLE SIZE DETERMINATION

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 (MBC) and EBC patients after Q3W treatment. With a CV of 60% assumed, a minimum of 80 patients per arm (i.e., a total of 160 patients) is needed to demonstrate C_{trough} non-inferiority (using a one-sided 95% confidence limit) with a power of 80% if the true means of the two formulations do not differ (GMR = 1). The sample size is increased to 200 (i.e., 100 patients per arm), as it is expected 80% of patients would be PK evaluable.

4. ANALYSIS SETS

The following populations are defined (Table 2).

Table 2 Analysis Populations

Population	Definition
Per Protocol PK Analysis Populations	The Per Protocol PK analysis populations will include all patients enrolled who adhered to the protocol. Patients will be assigned to treatment groups as treated. Exclusions from the Per Protocol PK analysis populations will be made for the following reasons: • patients are missing the C_{trough} pre-dose Cycle 8 PK sample, • patients with a Cycle 7 C_{trough} sample (pre-dose Cycle 8) 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 Cycle 7 dose delay of more than 7 days, • a Cycle 7 subcutaneous injection site other than thigh is used, • for Cycle 8 IV PK samples check if pre-dose and post-dose samples were switched, • assay error impacting C_{trough} (pre-dose Cycle 8) measurement. Patients will be excluded from the PK endpoints analyses according to exclusions defined above for pertuzumab and trastuzumab PK analyses separately. Pertuzumab Per Protocol PK (PPPP) analysis population will used for the co-primary endpoint of pertuzumab C_{trough} at pre-dose Cycle 8, while the trastuzumab Per Protocol PK (TPPP) analysis population will be used for the co-primary endpoint of trastuzumab C_{trough} at pre-dose Cycle 8. Excluded cases will be documented, including the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.
ITT (intent to treat) Population	The ITT population is defined as all randomized patients. Patients will be assigned to treatment groups as randomized by the IxRS.
Safety-evaluable Population	The safety analysis population will include all patients who receive at least one dose of study medication (i.e., chemotherapy, Perjeta and Herceptin IV, or the FDC). Patients who do not receive any dose of their study medication (i.e., chemotherapy, Perjeta and Herceptin IV, or the FDC) will be excluded from the safety-evaluable population. Patients will be assigned to treatment groups as treated.

C_{trough} = steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration); FDC = fixed dose combination; IV = intravenous; ITT = intent-to-treat; IxRS = interactive voice or web-based response system; PK = pharmacokinetics; PPPP = Pertuzumab Per Protocol PK; TPPP = trastuzumab Per Protocol PK.

5. STATISTICAL ANALYSES

5.1 GENERAL CONSIDERATION

PK analyses for pertuzumab and trastuzumab will be performed in Pertuzumab Per Protocol PK (PPPP) and trastuzumab Per Protocol PK (TPPP) analysis populations, respectively.

All efficacy analyses will be performed in the intent-to-treat (ITT) population, unless otherwise specified. Participants will be analyzed according to the treatment assigned at randomization by interactive voice/web-based response system (IxRS).

All safety analyses will be performed in the safety-evaluable population, unless otherwise specified. Participants will be analyzed according to the treatment they actually received.

Analyses of demographics and other baseline information will be based on the ITT population, and per treatment assigned by the IxRS.

The baseline value of any variable will be defined as the last available data point prior to the first administration of study drug.

5.2 PARTICIPANT DISPOSITION

The summary for study disposition, including number/percentage of participants who have completed the study vs. number/percentage of participants who have prematurely withdrawn from the study, as well as the primary reasons for withdrawal will be presented by treatment arm to which patients were randomized.

5.3 PRIMARY ENDPOINTS ANALYSES

5.3.1 Definition of Primary Endpoints

The co-primary endpoints of this study are observed pertuzumab and trastuzumab 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). Patients missing the C_{trough} (pre-dose Cycle 8) PK sample will be excluded from the analyses.

5.3.2 Main Analytical Approach for Primary Endpoints

The non-inferiority of the SC and IV dose of pertuzumab and trastuzumab will be assessed by a one-sided testing procedure. The C_{trough}SC/C_{trough}IV GMR of the SC dose relative to the IV dose will be estimated together with the two-sided 90% confidence interval (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 ≥ 0.8. A hierarchical testing procedure for the co-primary endpoints will be used to adjust for multiple comparison (Section 2).

5.4 SECONDARY ENDPOINTS ANALYSES

5.4.1 Secondary Efficacy Endpoints

There is no secondary efficacy endpoint pursued as part of the confirmatory hypotheses for which the type I error is controlled.

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 CI will also be calculated. The lower bound of the CI will reliably reflect the largest tpCR difference that could be considered unlikely. The observed tpCR difference and 95% CI will form the basis of a discussion around the differences in efficacy that can be ruled out. Patients with missing data for tpCR (i.e., do not undergo surgery or have an invalid tpCR assessment) will be included in the analysis and will be classed as non-responders.

In order to assess whether magnitude of the effectiveness of FDC differs according to patient subgroups, tpCR subgroup analyses will be performed for the randomization stratification factors using the categories defined in Section 1.2 , as well as for other disease-or patient-related prognostic or predictive factors, such as but not limited to:

- Age: <65, ≥ 65
- 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
- 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 with descriptive statistics summarizing tpCR rates and 95% CIs, by treatment arm.

For all time-to-event (TTE) endpoints, iDFS, iDFS including second primary non-breast cancer, EFS, EFS including second primary non-breast cancer, distant recurrence-free interval (DRFI), and OS described in Table 1, 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 (HR) and corresponding 95% CI will also be obtained using Cox regression models. Patients who are without the event defined for respective TTE endpoints will be censored at their last known date in the study and event free.

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 EFS and DRFI, data for patients who are randomized without any post-baseline assessments will be censored at the time of randomization plus 1 day.

Subgroup analyses for TTE endpoints will be performed in an exploratory manner in forest plots using the same disease-or patient-related prognostic or predictive factors as in the tpCR subgroup analyses.

5.4.2 Secondary Safety Endpoints

Safety will be evaluated by the use of descriptive analyses of incidence and severity of adverse events (AEs) and serious AEs (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 adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and adverse event severity will be graded according to the NCI-CTCAE, v4. Congestive heart failure (CHF), 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. 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 abnormalities will be defined based on local laboratory normal ranges and National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (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. 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 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 Standardised MedDRA Query (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. Please see Sections 5.1.1.1 and 5.2.5.2 in protocol for additional information about ARRs.

Cardiac-specific AEs will focus on the incidence of patients with heart failure (NYHA, 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:
    1. Definite cardiac death (due to heart failure, myocardial infarction, or documented primary arrhythmia); or
    2. 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 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 ≥ 10 percentage points below the baseline measurement and to an absolute LVEF value of < 50%

The assessment of the cardiac endpoint will be based on data from randomization until the start of any new therapy for recurrence of disease. Therefore, any asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF should be confirmed within approximately 3 weeks, even during follow-up phase.

Safety analyses will be performed at the primary and final analyses and may be performed at additional timepoint during the study as necessary.

5.5 EXPLORATORY ENDPOINTS ANALYSES

5.5.1 Exploratory PK Endpoints

The exploratory PK analyses (see Section 6.5.1 in protocol) will include characterization of the PK of pertuzumab and trastuzumab following FDC SC administration. PK parameters will be presented by listings and descriptive summary statistics including arithmetic mean, geometric mean, median, range, standard deviation and CV, and 95% CIs.

Exploratory PK analyses including population PK and exposure-response analyses will be assessed by the clinical pharmacology group as needed and analysis details will be provided in a separate PK analysis plan.

5.5.2 Exploratory Efficacy Endpoints

To further assess the tpCR endpoint, exploratory analyses will be conducted analyzing:

- Breast pathological complete response (bpCR), defined as eradication of invasive disease in the breast (i.e., ypT0/is, ypNx)

Analysis methods will be the same as those for the secondary tpCR endpoint (see Section 5.4.1).

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.

5.5.3 Exploratory Immunogenicity Endpoints

The immunogenicity analysis population will consist of all patients with at least one anti-drug antibody (ADA) assessment. 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 details 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).

5.5.4 Exploratory Biomarker Endpoints

Biomarker analyses will be exploratory and will assess correlations between biomarker status and efficacy and/or safety, including but not limited to the following outcomes:

- Association of HER2 immunohistochemistry (IHC) expression levels, HER2 results by in situ hybridization (ISH) including HER2 gene copy number/ratio with efficacy
- Evaluation of rates of concordance between local and central assessment of hormone receptor status

Descriptive statistics and similar methods as in the above sections will be applied to exploratory analyses as appropriate. In addition, various types of multivariate analyses may be conducted as the data indicate.

5.6 OTHER SAFETY ANALYSES

5.6.1 Extent of Exposure

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.

5.6.2 Adverse Events

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

In addition, AEs leading to discontinuation/dose modification of study treatment will be summarized by treatment arm.

5.6.3 Vital Signs

Vital signs (including systolic blood pressure, diastolic blood pressure, and pulse rate) and physical measurements (including body weight) 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.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for patient discontinuations from the study treatment and from the study will be listed and summarized.

In addition, major protocol deviations, including major deviations with regards to the inclusion and exclusion criteria, will be summarized by treatment arm.

Enrollment, study treatment administration, and major protocol deviations will be evaluated for their potential effects on the interpretation of study results.

5.7.2 Summaries 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 breast cancer history (including randomization stratification factors). Descriptive statistics (e.g., mean, median, standard deviation, 25th percentile, 75th percentile, and range) will be presented for continuous variables, and proportions will be presented for categorical variables.

Summaries will be presented by treatment group and separated where relevant into the neo-adjuvant period, adjuvant period and follow up period.

5.8 INTERIM ANALYSES

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

6. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

7. REFERENCES

Not Applicable.