# STATISTICAL ANALYSIS PLAN

A randomized, double-blind, parallel group, Phase III trial to compare the efficacy, safety, and immunogenicity of TX05 with Herceptin® in subjects with HER2 positive early breast cancer

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|---|---|
| **Protocol Title:** | A randomized, double-blind, parallel group, Phase III trial to compare the efficacy, safety, and immunogenicity of TX05 with Herceptin® in subjects with HER2 positive early breast cancer |
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Prepared by:

[redacted]

On behalf of:

Tanvex Biologics Corp.





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[redacted]

# CSR
# Statistical Analysis Plan (SAP)

## SIGNATURE PAGE FROM [redacted]

**Prepared [redacted] by:**

[redacted]

[redacted]

Date
(DD MMM YYYY)

**Reviewed [redacted] by:**

[redacted]

[redacted]

Date
(DD MMM YYYY)

## SIGNATURE PAGE FROM TANVEX

**Approved at Tanvex Biologics Corp. by:**

[redacted]

[redacted]

Date
(DD MMM YYYY)

## REVISION HISTORY

| Version/Date | Version name | Section | Changes implemented |
|---|---|---|---|
| Version 1.0/ 27-Jul-2018 | Initial approved version | N/A | N/A |
| Version 2.0/ 02-Sep-2019 | Final Version 2.0 | 8.5.1 Treatment duration | Removed duration of Epirubicin/Cyclophosphamide/Paclitaxel. |
| Version 2.0/ 02-Sep-2019 | Final Version 2.0 | 8.8.3 Clinical laboratory evaluations<br>8.8.5 Physical examinations<br>8.8.6 12-lead Electrocardiograms<br>8.8.7.3 ECOG | Removed all shift tables from baseline of cycle 1. |
| Version 2.0/ 05-Sep-2019 | Final Version 2.0 | 8.8.7.5 LVEF | Added shift table from baseline of cycle 5. |
| Version 2.0/ 16-Oct-2019 | Final Version 2.0 | LIST OF ABBREVIATIONS | Updated 'NaB' to 'Nab'. |
| Version 2.0/ 16-Oct-2019 | Final Version 2.0 | 3.1 General study design | Updated 'up to 10 treatment cycles' to 'up to 13 treatment cycles'. |
| Version 2.0/ 16-Oct-2019 | Final Version 2.0 | 3.3 Study treatments and assessments | Removed "bacteriostatic". |
| Version 2.0/ 16-Oct-2019 | Final Version 2.0 | 5 Sample size and power | Updated typo:<br>- pCSR' to 'pCR' in Table 5.1.<br>- trastzumab to trastuzumab. |
| Version 2.0/ 16-Oct-2019 | Final Version 2.0 | 7.1 Derived Variables | Separated baseline and change from baseline;<br>- Baseline:'Baseline of cycle 1'/ 'Baseline of cycle 5'<br>- Change from baseline: 'Change from cycle 1 baseline'/ 'Change from cycle 5 baseline'.. |
| Version 2.0/ 16-Oct-2019 | Final Version 2.0 | 7.2.2.2 Missing Causality and Severity for Adverse Events | Separated Causality imputation rule of AE is missing for cycle 1-4 and cycle 5-8. |
| Version 2.0/ 16-Oct-2019 | Final Version 2.0 | 8.8.1 Adverse events | 1. Specified cycle for AE tables.<br>2. Added AE tables for related to study drug. |

| | | | |
|---|---|---|---|
| | | | 3. Updated 'epirubicin and cyclophosphamide' to ' epirubicin and/or cyclophosphamide'. |
| Version 3.0/ 19-Nov-2019 | Final Version 3.0 | 8.8.7.5 LVEF | LVEF, add category 'Hyperdynamic' for value greater than 70%. |
| Version 3.0/ 16-Apr-2020 | Final Version 3.0 | 7.2.2.1 Partial Dates for Adverse Events | Updated imputation rule of AE start date. |
| Version 3.0/ 16-Apr-2020 | Final Version 3.0 | 8.8.1 Adverse events | Updated definition for 'TEAEs for Cycles 1-4' and 'TEAEs for Cycle 5-8'. |
| Version 3.0/ 12-Jun-2020 | Final Version 3.0 | 6.4 Per Protocol Population | Added to clarify protocol deviation criteria for PP set. |
| Version 3.0/4FEB2021 | Final Version 3.0 | 6.4 Per Protocol Population | Updated to clarify that those delay >8 weeks due to COVID 19 will not be excluded and those indetermined PCR will be excluded. |

## TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| ADA | Anti-drug antibodies |
| AE | Adverse event |
| BMI | Body mass index |
| BSA | Body surface area |
| CI | Confidence interval |
| CRF | Case report form |
| CS | Clinically Significant |
| CSR | Clinical Study Report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EOT | End of Treatment |
| ER | Estrogen receptor |
| ET | Early termination |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HER | Human epidermal growth factor receptor |
| HIV | Human immunodeficiency virus |
| ICH | International Council for Harmonization |
| IV | Intravenous |
| IWRS | Interactive web response system |
| LVEF | Left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified intent-to-treat |
| MRI | Magnetic resonance imaging |

| | |
|---|---|
| Nab | Neutralizing antibodies |
| NCS | Not Clinically Significant |
| NOAH | Neoadjuvant Herceptin |
| ORR | Objective response rate |
| pCR | Pathologic complete response |
| PK | Pharmacokinetic |
| PP | Per protocol |
| PR | Progesterone receptor |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RR | Risk Ratio |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SOC | System organ class |
| TEAE | Treatment-emergent adverse event |

# 1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol TX05-03 Final "A randomized, double-blind, parallel group, Phase III trial to compare the efficacy, safety, and immunogenicity of TX05 with Herceptin® in subjects with HER2 positive early breast cancer" dated 30Nov2017 and decision log ID #21 of "Action-Decision Log Tanvex TX05-03_03May2018" for CSR analysis. The table of contents and templates for the TFLs will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been in accordance with FDA regulations (CFR, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

All data analyses and generation of TFLs will be performed using SAS 9.4® or higher.

# 2 STUDY OBJECTIVES

## 2.1 Primary objective(s)

The primary objective of this study is to demonstrate the therapeutic equivalence of TX05 (proposed biosimilar trastuzumab) to Herceptin (trastuzumab) based on the pathologic complete response (pCR) rate following neoadjuvant chemotherapy, defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ypT0/Tis ypN0), in subjects with HER2 positive (HER2+) invasive EBC.

## 2.2 Secondary objective(s)

The secondary objective of this study is to compare objective response rate (ORR) between the 2 arms; immunogenicity, safety, and tolerability will also be assessed.

# 3 STUDY DESIGN

## 3.1 General study design

This is a randomized, double-blinded, parallel group, equivalence, multicenter Phase III study. The study will consist of a Screening period (Days -28 to 0), and 8 cycles of neoadjuvant treatment (Week 0 [Day 1] to Week 21), followed by surgery (3 to 7 weeks from the 1st day of the last cycle/last dose of study drug). Post-surgery, subjects may be eligible to enroll in a separate (extension) protocol to receive adjuvant treatment with trastuzumab (Herceptin or TX05) for up to 13 treatment cycles.

800 subjects with HER2+ EBC will be randomized (1:1) to receive up to 8 cycles of neoadjuvant chemotherapy as follows:

- IV epirubicin, 75 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$ every 3 weeks for 4 cycles

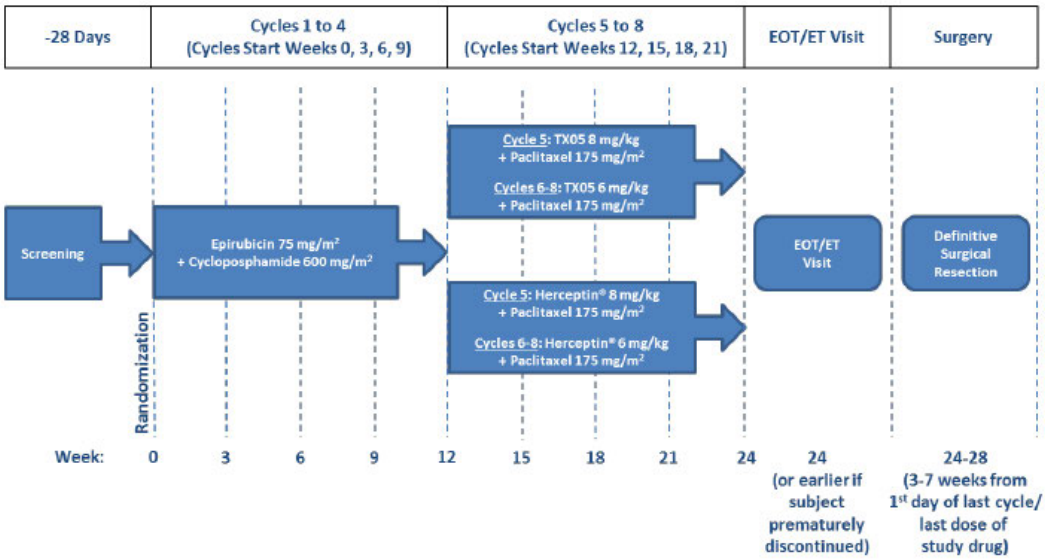
Followed by either:

- IV TX05 8 mg/kg loading dose then 6 mg/kg and paclitaxel 175 mg/m$^2$ every 3 weeks for 4 cycles.

OR

- IV Herceptin 8 mg/kg loading dose then 6 mg/kg and paclitaxel 175 mg/m$^2$ every 3 weeks for 4 cycles.

**Figure 3.1: Study Design Flow Diagram**



### 3.2 Randomization and blinding

Both randomization and blinding techniques will be used in this study to minimize bias. This is a double-blinded study and randomized treatment assignments will be blinded to the subject, investigator/study staff and Sponsor's study team conducting the study. The central pathology readers for pCR will also be blinded to study treatment. A computer generated randomization schema will be centrally available via interactive web response system (IWRS) to all sites that meet the requirements for participation in the study. Subjects will be randomized after the Screening Visit and prior to the treatment period. The randomization will be stratified by 'Hormone Receptor (HR) Status' and 'Tumor Stage', including: Strata 1: HR Positive and Tumor Stage II; Strata 2: HR Positive and Tumor Stage IIIa; Strata 3: HR Negative and Tumor Stage II; Strata 4: HR Negative and Tumor Stage IIIa with 1: 1 ratio. Randomization of eligible subjects is preferred no more than 4 business days before administration of first dose of study drug. At the initiation of the study, all sites will be instructed on how to use IWRS for breaking the blind, if necessary.

### 3.3 Study treatments and assessments

TX05 drug product is a sterile, preservative-free, lyophilized product in a 50 mL glass vial. Each vial contains 420 mg of TX05, sufficient to deliver 420 mg. After reconstitution with 20 mL of water for injection, the product formulation is 21 mg/mL TX05, 4.2 mM histidine/histidine hydrochloride, 50.4 mM trehalose, and 0.007% (w/v) polysorbate 20, pH 6.0. The formulation of the TX05 drug product is identical in composition to Herceptin. The selected components are well-known antibody stabilizers and the target pH is similar to other formulations of Ig-based drug products.

Subjects will receive up to 8 cycles of neoadjuvant chemotherapy as follows:

Cycles 1 to 4:

- Epirubicin 75 mg/m$^2$ by IV bolus infusion and cyclophosphamide 600 mg/m$^2$ by 30-minute IV infusion, on Day 1 of Cycle 1 and thereafter every 3 weeks until Cycle 4.

Followed by:

TX 05 Cycles 5 to 8:

- TX05 8 mg/kg body weight by 90-minute IV infusion and paclitaxel 175 mg/m$^2$ administered over 60 minutes by IV infusion (Cycle 5).
- TX05 6 mg/kg body weight by 60-minute IV infusion and paclitaxel 175 mg/m$^2$ administered over 60 minutes by IV infusion, on Day 1 of the treatment cycle (Cycles 6 to 8).

OR

Herceptin Cycles 5 to 8:

- Herceptin 8 mg/kg body weight by 90-minute IV infusion and paclitaxel 175 mg/m$^2$ administered over 60 minutes by IV infusion (Cycle 5).
- Herceptin 6 mg/kg body weight by 60-minute IV infusion and paclitaxel 175 mg/m$^2$ administered over 60 minutes by IV infusion, on Day 1 of the treatment cycle (Cycles 6 to 8).

A detailed description of procedures and assessments to be conducted during this study is summarized in the schedule of study assessments in Table 3.3.1 and schedule of blood sampling in Table 3.3.2 below.

**Table 3.3.1: Schedule of Study Assessments**

| Study Procedure | Screening (-28 days)[1] | Randomization[1] | Neoadjuvant Cycle (week) | | | | | | | | EOT/ET[2] | Surgery[3] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Epirubicin + Cyclophosphamide | | | | Trastuzumab + Paclitaxel | | | | | |
| | | | 1 (0) | 2 (3) | 3 (6) | 4 (9) | 5 (12) | 6 (15) | 7 (18) | 8 (21) | Week 24 | |
| **Visit Window (days)** | | | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 7 | |
| Informed consent[4] | X | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | |
| Medical & surgical history | X | | | | | | | | | | | |
| Physical examination[5] | X | | | | | | | | | | X | |
| Weight and BSA[6] | X | | X | X | X | X | X | X | X | X | | |
| Vital signs[7] | X | | X | X | X | X | X | X | X | X | X | |
| Pregnancy test[8] | X | | X | X | X | X | X | X | X | X | | |
| ECOG performance status | X | | X | X | X | X | X | X | X | X | X | |
| Eligibility criteria | X | | | | | | | | | | | |
| Histologically confirmed invasive breast cancer | X | | | | | | | | | | | |
| HER2 expression[9] | X | | | | | | | | | | | |
| ER & PR Testing[10] | X | | | | | | | | | | | |
| Clinical laboratory tests[11] | X | | X | X | X | X | X | X | X | X | X | |
| Viral disease screen[12] | X | | | | | | | | | | | |
| 12-Lead ECG | X | | | | | | X | | | | X | |
| LVEF (echocardiography or MUGA) | X | | | | | | X | | | | X | |
| Study drug administration[13] | | | X | X | X | X | X | X | X | X | | |
| Immunogenicity sampling[14] | | | | | | | X | | X | | X | |
| PK sampling[15] | | | | | | | X | X | X | X | X | |
| Tumor assessment[16] | X | | | | | | | | | | X | |
| AE assessment | | | X | X | X | X | X | X | X | X | X | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject compliance | | | X | X | X | X | X | X | X | X | | |
| Concomitant medication | | | X | X | X | X | X | X | X | X | X | |
| Definitive surgical resection[17] | | | | | | | | | | | | X |

AE: Adverse Event; BSA: Body Surface Area; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT/ET: End of Treatment/Early Termination; ER: Estrogen Receptor; HER: Human epidermal growth factor receptor; LVEF: Left ventricular ejection fraction; MUGA: Multi-gated acquisition; PK: pharmacokinetic; PR: Progesterone Receptor.

1. All Screening procedures, laboratory results, and repeat laboratory results must be completed and reviewed within the screening period prior to randomization. Randomization of eligible subjects is preferred no more than 4 business days before administration of first dose of study drug.
2. All subjects completing neoadjuvant treatment (and those prematurely discontinuing neoadjuvant treatment at any time) will attend an EOT/ET Visit 3 weeks after last administration of study drug. The allowable window for the EOT/ET Visit is ± 7 days.
3. Subjects will undergo a definitive surgical resection of their primary tumor 3 to 7 weeks from the 1st day of the last cycle/last dose of study drug.
4. Informed consent must be obtained prior to undergoing any study-specific procedure and may occur prior to the 28-day Screening period.
5. Complete physical examinations will be conducted at Screening and at the EOT/ET Visit. All other evaluations will be at the discretion of the investigator. Height will be recorded at Screening only.
6. Weight and BSA will be recorded at Screening and Day 1 of each cycle and as clinically indicated. The weight from Day 1 of Cycles 5, 6, 7, and 8 should be used to calculate the dosage of trastuzumab to be administered. The BSA from Day 1 of each cycle should be used to calculate the dosage of chemotherapy to be administered.
7. Temperature, blood pressure, pulse rate, and respiratory rate will be recorded at each timepoint.
8. Subjects of childbearing potential will have a blood serum pregnancy test at Screening. A urine pregnancy test will also be performed prior to each treatment cycle to exclude potential pregnancy.
9. HER2-positive tumor status for study eligibility will be based on the test performed by the local laboratory at the time of diagnosis or as determined by the central laboratory where not known locally. HER2 status that was determined locally will be confirmed by the central laboratory. Tumor tissue sample must be available for central analysis.
10. Only for subjects with unknown ER and/or PR status.
11. Clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be performed by local laboratories.
12. Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and/or human immunodeficiency virus (HIV) to be conducted by local laboratory only in countries where regulations mandate testing or if warranted by known subject history.
13. Subjects will receive 8 cycles of neoadjuvant chemotherapy: Cycles 1-4: epirubicin 75 mg/m$^2$ by IV bolus infusion and cyclophosphamide 600 mg/m$^2$ by 30-minute IV infusion, on Day 1 of the treatment cycle and thereafter every 3 weeks until Cycle 4. Cycles 5 to 8: TX05 or Herceptin 8 mg/kg body weight by 90-minute IV infusion and paclitaxel 175 mg/m$^2$ administered over 60 minutes by IV infusion followed by TX05 of Herceptin 6 mg/kg body weight by 60-minute IV infusion and paclitaxel 175 mg/m$^2$ administered over 60 minutes by IV infusion, on Day 1 of the treatment cycle and thereafter every 3 weeks until Cycle 8.
14. Serum samples for detection of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) will be collected prior to initiation of infusion at Cycle 5 (Week 12), prior to infusions at Cycle 7 (Week 18), and the EOT/ET Visit. For those subjects who terminate the study early before Cycle 5, there is no need to take the EOT/ET ADA sample.
15. For 100 subjects in each of the 2 treatment arms (200 subjects total), PK samples will be taken prior to initiation of infusion at Cycle 5 (Week 12), Cycle 6 (Week 15), Cycle 7 (Week 18), Cycle 8 (Week 21), and the EOT/ET Visit. PK samples will be taken for assessment of trough serum concentration ($C_{trough}$).
16. Computed tomography (CT) scan of chest or magnetic resonance imaging (MRI) of chest (only if CT scan cannot be performed) and bilateral mammography or ultrasound of the breast required at Screening for all subjects, within 6 weeks prior to randomization. Unilateral repeat mammography or ultrasound of the breast must be performed at the EOT/ET Visit and as clinically indicated. Radiographic assessments obtained per the subject's standard of care (SOC) prior to randomization do not need to be repeated if (1) they were obtained within 6 weeks prior to randomization, (2) they were performed using the method requirements outlined in Response Evaluation Criteria in Solid Tumors

(RECIST version 1.1) (3) the same imaging technique should be used throughout the study for the subject, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as SOC is available in the subject's source notes. Final disease assessment at the EOT/ET Visit will include repeat CT scan of chest or MRI of chest (only if CT scan cannot be performed) and unilateral mammography or ultrasound of breast. Assessments are not to be scheduled based on the scheduled calendar date of the EOT/ET Visit.

17. Subjects will undergo a definitive surgical resection of their primary tumor 3 to 7 weeks from the 1st day of the last cycle/last dose of study drug, i.e. lumpectomy or mastectomy with sentinel node (SN) biopsy or axillary lymph node dissection (ALND). Pathology of the tumor sample and pathologic response will be assessed locally and reviewed centrally by a qualified pathologist.

**Table 3.3.2: Schedule of Blood Sampling**

| Assessment | Screening | Cycle 1 (Week 0) | Cycle 2 (Week 3) | Cycle 3 (Week 6) | Cycle 4 (Week 9) | Cycle 5 (Week 12) | Cycle 6 (Week 15) | Cycle 7 (Week 18) | Cycle 8 (Week 21) | EOT/ ET Visit |
|---|---|---|---|---|---|---|---|---|---|---|
| Hematology | 4 mL | 4 mL | 4 mL | 4 mL | 4 mL | 4 mL | 4 mL | 4 mL | 4 mL | 4 mL |
| Clinical Chemistry | 4.5 mL | 4.5 mL | 4.5 mL | 4.5 mL | 4.5 mL | 4.5 mL | 4.5 mL | 4.5 mL | 4.5 mL | 4.5 mL |
| Pharmacokinetics (100 subjects per treatment arm) | | | | | | 7 mL | 7 mL | 7 mL | 7 mL | 7 mL |
| Immunogenicity | | | | | | 7 mL | | 7 mL | | 7 mL |

Additional blood tests may be performed for viral disease screen and pregnancy testing (if required at Screening) and per SOC, at the investigator's discretion for the purpose of planning treatment administration, dose modification (Appendix 1), following AEs, or as clinically indicated.

# 4 STUDY ENDPOINTS

## 4.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is the proportion of subjects in each treatment arm who achieve pCR, defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ypT0/Tis ypN0). Pathology of the tumor sample and pathologic response will be assessed locally and reviewed centrally by a qualified pathologist. The primary efficacy analysis will be based on the central pathological review.

## 4.2 Secondary efficacy endpoint(s)

ORR, defined as the percentage of subjects having Complete or Partial Response at the EOT/ET Visit, according to RECIST version 1.1 (see Appendix 2), as assessed by the investigator.

## 4.3 Immunogenicity Assessments

- Incidence of ADA.
- Incidence of Nab.

## 4.4 Safety endpoint(s)

- Treatment-emergent AE (TEAE) and serious AE (SAE).
- Death
- Clinical laboratory parameters
- Vital signs
- 12-Lead ECG cardiac ejection fraction
- Physical examination

# 5 SAMPLE SIZE AND POWER

The primary efficacy endpoint is the proportion of subjects in each treatment arm who, achieve pCR. For the calculation of the equivalence margin, neoadjuvant Herceptin[1, 2, 3, 4, 5] studies of 'trastuzumab + chemotherapy (anthracyclines and/or taxanes based)' vs 'chemotherapy (anthracyclines and/or taxanes-based) alone' were considered. pCR rates were reported for 4 studies with HER2-positive subjects in early or locally advanced breast cancer. The rate of pCR for each study is provided in the table below.

**Table 5.1: Rates of pCR from Neoadjuvant Herceptin Studies**

| Name | Trastuzumab + Chemotherapy (T + C) | Chemotherapy Alone (C) |
|---|---|---|
| NOAH (MO16432) [1,2] | (n =115)<br>46 (40.0%) | (n=116)<br>24 (20.7%) |
| Buzdar[3] | (n=23)<br>15 (65.2%) | (n=19)<br>5 (26.3%) |
| Pierga[4] | (n=62)<br>16 (25.8%) | (n=58)<br>11 (19.0%) |
| ABCSG-24[5] | (n=44)<br>17 (38.6%) | (n=49)<br>13 (26.5%) |
| Combined risk ratio of pCR[a]<br>95% CI (T+C:C) | 1.755[b]<br>[1.317, 2.337] | |

C: Chemotherapy; CI: Confidence Interval; NOAH: NeOAdjuvant Herceptin; T: Trastuzumab.
a. Using the inverse variance-weighed method
b. Chi square test was used to test for homogeneity at 0.05 level (Q=1.817, p=0.611).

Based on the results of meta-analysis, the combined risk ratio for trastuzumab + chemotherapy over chemotherapy alone is estimated to be 1.755. The equivalence margin is determined as [0.755, 1.325] to protect 50% of the effect size based on a log scale (upper equivalence limit is exp[0.5×ln(1.755)=1.325]).

With 370 subjects per treatment group, there is 85% probability that the observed two-sided 95% CI of the risk ratio of TX05 + chemotherapy to Herceptin + chemotherapy will lie within [0.755, 1.325] assuming a 5% type 1 error rate, a pCR rate of 44.6% in both treatment groups, and that the actual risk ratio is 1.00. Allowing for 7.5% losses to follow-up, at least 400 subjects per arm, 800 in total, will be randomized

# 6 ANALYSIS POPULATIONS

## 6.1 Enrolled population

The enrolled population will include the subjects who have signed-off the informed consent form and performed any assessment at the screening visit.

## 6.2 All randomized population

The all randomized population will include the subjects who are randomized into the study regardless taking the study drug. It will be used for the data listings unless specified otherwise.

## 6.3 Modified Intent to Treat Population

The modified intent-to-treat (mITT) population will include all subjects who are randomized into the study and receive at least 1 dose of TX05 or Herceptin. A sensitivity analysis of the primary efficacy variable and the primary analysis of the secondary efficacy endpoint will be performed using the mITT population.

## 6.4 Per Protocol Population

The per protocol (PP) population will include all subjects who meet all of the following criteria:

- Randomized and receive at least one dose of study drug, either TX05 or Herceptin.
- No major protocol deviations that impact the efficacy endpoints. The following major protocol deviations are considered to exclude from Per Protocol Population.
  - Not meet the following HER2 results.
    - A central HER2 result of Positive.
    - A local HER2 result of Positive and no central HER2 result."
  - Failed to complete 8 cycles of treatment.
  - Surgery performed > 8 weeks from last dose not based on COVID-19 delays. (Those delay due to COVID-19 will not be excluded.)
  - Tumor size < 2 cm or not measurable.
  - Invasive breast carcinoma not histologically confirmed.
  - Presence of metastatic disease, bilateral lesions or inflammatory breast cancer.
  - Not evaluable (cannot be assessed or indetermined) for pCR assessment as reported by central lab.
  - Subjects that receive incorrect IP/comparator (only TX05 or Herceptin) assigned to subject (for example subject is assigned to TX05-03 arm and receives Herceptin)

A central/local HER2 test results and a central pCR assessment deviations will be checked in captured datasets. Other above protocol deviations will be described in Protocol Deviation Criteria Form (CTM002-SOP-T01).

- An adequate tumor sample by definitive surgical resection of their primary tumor.

The primary efficacy analysis will be carried out using the PP population.

## 6.5 Safety Population

The safety population will include all subjects who are randomized into the study and have received at least one dose of study drug (TX05 or Herceptin). The safety population will be used for safety and immunogenicity endpoints.

# 7 STATISTICAL CONSIDERATIONS AND ANALYSIS

## 7.1 Derived Variables

The table below provides the list of derived variables for Demographic and baseline characteristics, various duration derivations, baseline derivations and other important derivations applicable for this study.

| Variables | Formula |
|---|---|
| **Demographic and Baseline characteristics** | |
| Age at informed consent (in years) | year of informed consent – year of birth + 1 |
| **Date of Administration of Study Drug** | |
| First dose date of Cycle 1 | The minimum date of non-zero dose of Epirubicin or Cyclophosphamide |
| First dose date of Cycle 5 | The minimum date of non-zero dose of TX05/Herceptin or paclitaxel |
| First date of administration of Epirubicin | The minimum date of non-zero dose of Epirubicin (First dose of Epirubicin) |
| Last date of administration of Epirubicin | The maximum date of non-zero dose of Epirubicin (Last dose of Epirubicin) |
| First date of administration of Cyclophosphamide | The minimum date of non-zero dose of Cyclophosphamide (First dose of Cyclophosphamide) |
| Last date of administration of Cyclophosphamide | The maximum date of non-zero dose of Cyclophosphamide (Last dose of Cyclophosphamide) |
| First date of administration of TX05/Herceptin | The minimum date of non-zero dose of TX05/Herceptin) (First dose of TX05/Herceptin) |
| Last date of administration of TX05/Herceptin | The maximum date of non-zero dose of TX05/Herceptin) (Last dose of TX05/Herceptin) |
| First date of administration of Paclitaxel | The minimum date of non-zero dose of Paclitaxel (First dose of Paclitaxel) |
| Last date of administration of Paclitaxel | The maximum date of non-zero dose of Paclitaxel (Last dose of Paclitaxel) |
| **Baseline Derivations** | |
| Baseline of cycle 1 | Last observation prior to or on the date of the first dose of Epirubicin/Cyclophosphamide on cycle 1 |
| Baseline of cycle 5 | Last observation prior to or on the date of the first dose of TX05/Herceptin/Paclitaxel on cycle 5 |

| | |
|---|---|
| Change from cycle 1 baseline | Post baseline value – Baseline of cycle 1 |
| Change from cycle 5 baseline | Post baseline value – Baseline of cycle 5 |
| **Study day** | |
| Study day | Event or Assessment date – First dose date of Cycle 1 +1<br>The study day will be displayed in data listings. |

## 7.2 Handling of missing data and outliers

### 7.2.1 Missing data analysis methods

The subjects who do not have pCR or ORR results will be assessed as non-responders for the mITT analysis of the efficacy endpoints. Tipping point analysis will be performed for primary efficacy endpoint to explore the robustness of statistical results.

### 7.2.2 Handling of missing or incomplete dates

#### 7.2.2.1 Partial Dates for Adverse Events

When only day is missing:

If it is the end date of an AE, the last day of the month will be used.

For start date of an AE:

- If AE start month and year is prior to the month and year for the first dose date of Cycle 1, impute the AE start day as 1

  Otherwise,

- If the AE stop date is prior to first dose date of Cycle 1, impute the AE start day as 1
- If the AE stop date is on or after first dose date of Cycle 1 medication but before first dose date of Cycle 5:
  - If month and year of onset date are the same as month and year of the first dose date in Cycle 1, impute AE start day as day of first dose date in Cycle 1
  - Else if the month and year of onset date are after the month and year of the first dose date in the Cycle 1, impute AE start day as 1
- If the AE stop date is on or after first dose date of Cycle 5 or if AE stop date is completely missing:
  - For AEs occurred in Cycle 1 - 4 or ongoing AE re-entered into Cycle 5:
    - If month and year of onset date are the same as month and year of the first dose date in Cycle 1, impute AE start day as day of first dose date in Cycle 1
    - Else impute AE start day as 1
  - For new AEs (not ongoing AE carried from Cycle 1 - 4) entered into Cycle 5:

- If month and year of onset date are the same as month and year of the first dose date in Cycle 5, impute AE start day as day of first dose date in Cycle 5
- Else impute AE start day as 1

When only day and month are missing:

If it is the end date of an AE, December 31st of the year will be used.

For start date of an AE:

- If the year of the AE onset date is prior to the year of the first dose date in Cycle 1, impute AE start month and day as January 1st

Otherwise,

- If AE stop date is prior to first dose of Cycle 1, impute the AE start month and day as January 1st
- If the AE stop date is on or after first dose of Cycle 1 but before first dose of Cycle 5:
  - If the year of onset date is the same as the year of the first dose date in Cycle 1,

    impute the AE start month and day as the month and day of the first dose date in Cycle 1.
  - Else impute AE start month and day as January 1st
- If the AE stop date is on or after first dose of Cycle 5 or AE stop date is completely missing:
  - For AEs occurred in Cycle 1 - 4 or ongoing AE re-entered into Cycle 5:
    - If the year of onset date is the same as the year of the first dose date in Cycle 1, impute the AE start month and day as the month and day of the first dose date in Cycle 1
    - Else impute AE start month and day as January 1st
  - For new AE (not ongoing AE carried from Cycle 1 - 4) entered into Cycle 5:
    - If the year of onset date is the same as the year of the first dose date in Cycle 5, impute the AE start month and day as the month and day of the first dose date in Cycle 5
    - Else impute AE start month and day as January 1st

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. For this type of AE, if it has partial AE stop date, compare the AE stop date to the first dose date in Cycle 1 and Cycle 5. If the AE stop date is before the first dose date of Cycle 1 then the AE should be considered as a pre-treatment AE. If the AE stop date is on or after the first dose date in Cycle 1 but before the first dose date of Cycle 5, the AE will be considered TEAE for Cycle 1- 4. Otherwise, if the AE stop date is on or after the first dose date in Cycle 5 or is an ongoing AE, the AE will be considered as TEAE for Cycle

5 - 8; if the AE stop date is on or after the first dose date in Cycle 5 and the given AE is new event (not ongoing AE carried from Cycle 1- 4), the AE will be considered as TEAE for Cycle 5 - 8 only.

For records with partial AE start date, the imputed AE start date will be used in the treatment emergent AE determination.

#### 7.2.2.2 Missing Causality and Severity for Adverse Events

When the causality of the AE is missing:

- If the causality of AEs is missing, causality will not be imputed for AEs prior to the first dose of Cycle 1
- If the causality of AEs is missing during Cycle 1 – Cycle 4, Causality will be imputed as "Possibly related" to Epirubicin/Cyclophosphamide for AEs which occurred started after the first dose of Cycle 1 for Epirubicin/Cyclophosphamide before the first dose of Cycle 5.
- If the causality of AE is missing after the first dose of Cycle 5 for TX05/Herceptin/Paclitaxel, Causality will be imputed as "Possibly related" to TX05/Herceptin/Paclitaxel for AEs which occurred started after the first dose of Cycle 5 for TX05/Herceptin/Paclitaxel.

When the severity of AEs is missing:

- Prior to study treatment: severity will not be imputed.
- During study treatment: missing severity will be imputed as severe.

#### 7.2.2.3 Missing or partial dates for concomitant medication

When only day is missing:

- If it is the start date of the medication prior to the first dose of Cycle 1, the first day of the month will be used.
- If it is the start date of the medication and the new record (not ongoing medication from Cycle 1 - 4):
    - If month and year is equal to the month and year of the first dose of Cycle 1, then the day of the first dose in Cycle 1 will be used;
    - Else the first day of the month will be used.
- If it is the end date of the medication, then the last day of the month will be used.

When day and month are missing:

- If it is the start date of the medication prior to the first dose of Cycle 1, January 1st of the year will be used.
- If it is the start date of the medication and the new record (not ongoing medication from Cycle 1 - 4):

- If year is equal to the year of first dose in Cycle 5, then the day and month of the first dose in Cycle 5 will be used;
- Else January 1st of the year will be used,

- If it is the end date of the medication, then December 31st of the year will be used.

If Year of medication start date is missing, no imputation will be done.

# 8 STATISTICAL METHODS

## 8.1 General statistical conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

All individual data as well as results of statistical analyses, whether explicitly discussed in the following sections or not, will be presented in individual subject data listings and statistical summary tables.

In general, continuous variables will be summarized using the following standard descriptive summary statistics: number of observations, arithmetic mean, standard deviation, minimum, median, and maximum. Categorical variables will be displayed by means of frequency tables including percentages. Subjects will be assigned to treatment groups "as randomized" for efficacy analyses, but "as treated" for all other analyses. For these other analyses, if there are any cases where subjects received both drugs, they will be assigned to the treatment initially given.

Given the design of the study, there are two types of baseline, defined as follows:

Baseline of cycle 1 (whole study): the last non-missing assessment with a collection date prior to the first dose date of epirubicin or cyclophosphamide.

Baseline of cycle 5 (TX05/Herceptin): the last non-missing assessment with a collection date prior to the first dose date of TX05/Herceptin and paclitaxel.

Those two types of baseline will be analyzed separately. For change from baseline regarding the test values, baseline of cycle 1 will be used for test values collected during cycle 1 – cycle 8, baseline of cycle 5 will be used for test values collected during cycle 5 – cycle 8.

## 8.2 Subject disposition

Subject disposition information will be summarized by treatment group and overall. The data summary will contain the following information:

- Number of subjects screened
- Number of subjects randomized
- Number of subjects treated
- Number and percent of subjects receiving study drug (TX05 or Herceptin)
- Number and percent of subjects in each analysis set (mITT, PP, safety)
- Number and percent of subjects completing the study/withdrawing early (including withdrawal reason)

A listing will be prepared to present data concerning subject disposition.

Subject allocation by site will be summarized.

### 8.3 Protocol deviations

The number of patients excluded from the PP analysis set and reasons for exclusion will be summarized by treatment group and overall.

Population membership details will be listed, including reason for exclusion from each population.

Subjects with study protocol deviations will be summarized by type of violation (major or non-major) and listed by treatment and site.

A listing will include the inclusion/exclusion criteria violated at Screening and at Baseline Visits, as well as other protocol deviations identified based on data recorded on the CRF.

### 8.4 Demographics and baseline characteristics

#### 8.4.1 Demographics

Demographic and baseline characteristics will be analysed in a descriptive fashion and results will be presented overall and by treatment group.

Sex, race, and ethnicity as categorical variables will be summarized using frequency count and percentages.

Age, height, weight and BSA as continuous demographic variables will be summarized by descriptive statistics.

Demographics will be listed for all randomized subjects.

#### 8.4.2 Baseline and disease characteristics

The categorical baseline characteristics such as estrogen receptor (ER) status, progesterone receptor (PR) status, hormone receptor (HR) status, tumor stage, ECOG performance status, Baseline Overall Interpretation of ECG, Viral disease (HBsAg, HBcAb, HCV, and HIV), breast cancer diagnosis (stage at initial diagnosis, stage at screening, histopathological classification at screening, HER2 status based on local determination and central review separately) will be summarized using frequency counts and percentage by treatment group. Baseline is defined as baseline of cycle 1.

Baseline characteristics will be listed for all randomized subjects.

#### 8.4.3 Medical history

A summary of medical history will be presented by system organ class (SOC) and preferred terms (PTs) using Medical Dictionary for Regulatory Affairs® (MedDRA). Medical history will be listed by subject.

#### 8.4.4 Prior and concomitant medications and surgeries/procedures

If the start date of a medication (including the imputed start date if applicable) is prior to first dose date of Cycle 1 or if the start date of the medication is missing, then the medication will be classified

as a prior medication.

Concomitant medication is classified as follows:

- For the concomitant medication for Cycle 1 - 4, if start data of a medication (including the imputed end date, if applicable) is missing or on or before the first dose date of Cycle 5 and the end date of a medication (including the imputed end date, if applicable) is on or after the first dose date of Cycle 1, or if the end date of the medication is missing;
- For the concomitant medication for Cycle 5 - 8, if the start date of medication is missing or on or before the first dose date of Cycle 5 and end date of medication is missing or on or after the first dose date of Cycle 5.

Prior and concomitant medications, coded using the most recent version of the WHO Drug Dictionary, will be summarized by treatment group and overall. The numbers of subjects using concomitant medications will be categorized by drug classification (Anatomical Therapeutic Chemical1) and PT. Concomitant medications will be listed.

Concomitant Surgeries / Procedures will be listed appropriately.

Breast tumor surgery will be summarized by treatment group and overall. The data summary will contain the following information:

- Number and percent of subjects performed surgery
- Number and percent of subjects did not perform surgery (including the reason)
- Breast surgery (Lumpectomy, Mastectomy and Other)
- Axilla surgery (Sentinel node resection, Axillary lymph node dissection and Other)
- Surgery outcome (Unresected, Resected, Partially resected and Not found)
- Pathological response (Complete pathological response, Partial pathological response and No pathological response)

Surgery will be listed for all randomized subjects.

### 8.5 Extent of exposure

The extent of exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed.

Treatment exposure will be presented for Epirubicin, Cyclophosphamide, TX05/Herceptin and Paclitaxel separately using the safety population and will be listed appropriately.

#### 8.5.1 Treatment duration

Descriptive statistics will be provided by treatment for the following:

- Number of cycles of Epirubicin
- Number of cycles of Cyclophosphamide

- Number of cycles of TX05/Herceptin
- Number of cycles of Paclitaxel
- Duration of TX05/Herceptin exposure (weeks)

Durations (weeks) are defined as the following,

- Duration of TX05/Herceptin exposure (weeks) = (Last date of administration of TX05/Herceptin – First date of Administration of TX05/Herceptin+ 21)/7

### 8.5.2 Cumulative Dose

Cumulative dose is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatments. For patients who do not receive any drug, the cumulative dose will be set to zero

- Total Epirubicin dose administered (mg and mg/$m^2$)
- Total Cyclophosphamide dose administered (mg and mg/$m^2$)
- Total TX05/Herceptin dose administered (mg and mg/kg)
- Total Paclitaxel dose administered (mg and mg/$m^2$)

### 8.5.3 Relative Dose Intensity

Relative dose intensity is defined as following,

- Relative Dose Intensity of Epirubicin = ([total Epirubicin dose administered in mg/$m^2$]/ [planned total Epirubicin dose])*100
- Relative Dose Intensity of Cyclophosphamide = ([total Cyclophosphamide dose administered in mg/$m^2$]/ [planned total Cyclophosphamide dose])*100
- Relative Dose Intensity of TX05/Herceptin = ([total TX05/Herceptin dose administered in mg/kg]/ [planned total TX05/Herceptin dose])*100
- Relative Dose Intensity of Paclitaxel= ([total Paclitaxel dose administered in mg/$m^2$]/ [planned total Paclitaxel dose])*100

where planned total dose is the prescribed starting dose * number of cycles of Epirubicin (mg/$m^2$), Cyclophosphamide (mg/$m^2$), TX05/Herceptin (mg/kg) or Paclitaxel (mg/$m^2$) respectively.

In addition, number and percentage will be provided for the subjects with relative dose intensity <50, 50-<70, 70-<90, 90-<110 and ≥110.

## 8.6 Efficacy analyses

### 8.6.1 Analysis methods

The analyses of the primary and secondary endpoints will be performed using the mITT population and the PP population.

#### 8.6.1.1 Multiplicity

Not applicable.

#### 8.6.1.2 Treatment by center interaction analysis (multi-center study)

Not applicable.

### 8.6.2 Analysis of primary efficacy endpoint(s)

The primary efficacy endpoint is the proportion of subjects in each treatment arm who, based on the central pathological review, achieve pCR, assessed by central reading, defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ypT0/Tis ypN0).

Two one-sided hypothesis tests will be performed in the study for pCR in order to show that TX05 is equivalent to Herceptin:

TEST 1: $H_{0a}$: $\theta_1 / \theta_2 > 1.325$ vs. $H_{1a}$: $\theta_1 / \theta_2 < 1.325$

TEST 2: $H_{0b}$: $\theta_1 / \theta_2 < 0.755$ vs. $H_{1b}$: $\theta_1 / \theta_2 > 0.755$

Where θ1 is the proportion of pCR for subjects randomized to TX05 group, θ2 is the proportion of pCR for subjects randomized to Herceptin. Justification of equivalence margin [0.755, 1.325] is described in the Section 5. Equivalence will be concluded if the 95% CI of the risk ratio is completely contained within the pre-defined interval [0.755, 1.325].

Frequency and percentage of subjects who meet the pCR criteria will be summarized in each treatment group. The primary analysis for pCR by central pathological review will be performed using the PP population. RR and its 95% CI will be provided and estimated. Asymptotic method will be applied to compute the confidence interval using standard normal percentile. To assess the robustness of the primary efficacy analysis, the primary efficacy variable will be evaluated in a sensitivity analysis using the mITT population. Subjects who are included in the mITT population, but do not have efficacy assessments will be assessed as non-responders.

Sensitivity analyses using log-binomial regression will be performed using subjects from the mITT and PP populations[6]. Treatment group and the stratification factors ('Hormone Receptor (HR) Status' and 'Tumor Stage') will be included as factors and pCR by central pathological review result will be the response variable. The 95% confidence interval of the RR will be computed. In case of failure

of convergence using log-binomial regression model, modified poisson regression will be applied instead, if convergence of poisson regression model is not met, the stratified mantel-haenszel chi-square statistic will be performed alternately. Stratification factors ('Hormone Receptor (HR) Status' and 'Tumor Stage') will be included as the controlled categorical factors.

An additional sensitivity analysis using the tipping point approach will be performed with the mITT population as performed by the FDA for the CT-P13 biosimilar study[7]. Tipping point analysis is one of the multiple imputation methods under the missing not at random assumption. Tipping point analysis will be used to explore the sensitivity of statistical results by shifting the response rate in subjects who have been withdrawn. The nominal list of imputing the pCR rate will be determined based on the data such as considering pCR rate of completers and withdrawer of each treatment groups. The subjects with missing pCR will be imputed either responder or non-responder based on the listed pCR rate. 1000 complete datasets will be generated and CIs will be constructed for every nominal pCR rate accordingly. It is repeated by listed pCR rates.

Listings will be produced for both investigator assessment and central review.

### 8.6.3 Analysis of secondary efficacy endpoint(s)

The secondary efficacy endpoint is:

- ORR, defined as the percentage of subjects having Complete or Partial Response at the EOT/ET Visit, according to RECIST version 1.1 (see Appendix 2), as assessed by the investigator.

ORR and the individual rates for CR, PR, SD, PD will be summarized descriptively using the frequency count and the percentage of subjects in each treatment group. The RR and its 95% CI will be estimated for ORR in the same way as for the primary efficacy variable. The primary efficacy analysis for the secondary efficacy endpoint will be carried out using the mITT population. A sensitivity analysis will be performed using the PP population.

Listings will be produced for tumor assessment.

## 8.7 Immunogenicity analyses

Immunogenicity data (ADA and Nab) will be summarized and analysed descriptively for each scheduled protocol assessment time-point. A shift table from baseline (baseline of cycle 5) to each scheduled protocol assessment time-point as well as overall will be provided by treatment group. Overall positive response is defined as negative at baseline and positive at least one positive at subsequent time point. The analysis will be performed with the safety population.

Immunogenicity data (ADA and Nab) will be listed.

### 8.8 Safety analyses

The safety parameters will include the following:

- TEAE and SAE
- Death
- Clinical laboratory parameters
- Vital signs
- 12-Lead ECG
- Physical examination

These analyses will be performed using the safety population.

#### 8.8.1 Adverse events

TEAEs will be described using descriptive statistics, and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and MedDRA preferred term, Severity of TEAEs will be graded according to CTCAE, by treatment group and overall.

Treatment-emergent AEs are defined as AEs occurring during or after the initial dose of drug in related Cycle. Adverse events documented prior to the initial dose cannot be classified as TEAEs unless there is a worsening in severity during or after the initial dose of study drug. Given the design of the study and the way AEs are collected, there are two types of TEAEs, defined as follows:

TEAEs for Cycles 1 - 4: AEs newly occurring on or after the first dose of epirubicin or cyclophosphamide and before the first dose of the TX05/Herceptin or Paclitaxel, or events newly occurring on or after the first dose of epirubicin or cyclophosphamide and within the last dose of epirubicin or cyclophosphamide in subjects that discontinue early from the study. Or worsening in severity on or after Day 1 of Cycle 1 and before Day 1 of Cycle 5. Or worsening in severity on or after Day 1 of Cycle 1 and within the last dose of epirubicin or cyclophosphamide in subjects that discontinue early from the study.

TEAEs for Cycles 5 - 8: AEs newly occurring on or after the first dose of TX05/Herceptin or Paclitaxel, or worsening in severity during or after Day1 of Cycle 5.

The overall incidence of TEAEs with all causalities will be summarized by treatment group and overall. The number and percent subjects will be reported in each of the categories: TEAEs, study drug related TEAE, TEAEs leading to study drug withdrawal, TEAEs leading to death, serious TEAEs, study drug related serious TEAE serious TEAEs leading to study drug withdrawal, and serious TEAEs leading to death.

Summary tables for overview TEAEs, TEAEs leading to study drug withdrawal, TEAEs leading to death, serious TEAEs leading to study drug withdrawal, and serious TEAEs leading to death will be provided for Cycle 1 - 4 for all randomized subjects, and Cycle 5 - 8 for all safety subjects.

Summary tables for TEAEs by system organ class and preferred term, TEAEs by maximum severity, serious TEAEs by system organ class and preferred term will be provided for Cycle 5 - 8 for all safety subjects.

Summary tables for TEAEs related to study drug (TX05/Herceptin) by system organ class and preferred term, TEAEs related to study drug (TX05/Herceptin) leading to study drug withdrawal, TEAEs related to study drug (TX05/Herceptin) leading to death, TEAEs related to study drug (TX05/Herceptin) by maximum severity, serious TEAEs related to study drug (TX05/Herceptin) by system organ class and preferred term, serious TEAEs related to study drug (TX05/Herceptin) leading to study drug withdrawal, serious TEAEs related to study drug (TX05/Herceptin) leading to death, serious TEAEs related to study drug (TX05/Herceptin) by maximum severity.

In summaries by SOC and PT, adverse events will be sorted by decreasing frequency within each SOC and PT according to the alphabetically order of total. In summaries by PT, AEs will be sorted by decreasing frequency according to the alphabetically order of alphabetically order of total.

Where a subject has the same adverse event, based on preferred terminology, reported multiple times in the treatment period, the subject will only be counted once at the preferred terminology level in adverse event frequency tables.

Where a subject has multiple adverse events within the same system organ class in the treatment period, the subject will only be counted once at the system organ class level in adverse event frequency tables.

When reporting adverse events by severity, in addition to providing a summary table based on the event selection criteria detailed above, summary table will also be provided, only the most severe occurrence will be included in the incidence.

All AEs will be listed. Additional listings will include AEs reported as reasons for discontinuation/death, and serious AEs.

### 8.8.2 Death

Listings will be produced for death with primary cause.

### 8.8.3 Clinical laboratory evaluations

Clinical safety laboratory data will be presented by treatment group and overall for each scheduled visit. For laboratory tests with quantitative values, descriptive statistics (number of subjects, mean, median, SD, min, and max) of the observed values and changes from baseline (baseline of cycle 1) at each scheduled visit will be reported. Change from baseline (baseline of cycle 5) laboratory data will be presented by treatment group and overall from cycle 5 for each scheduled visit. For laboratory tests with categorical values, the number and percent of subjects in each category will be summarized

by treatment group at each scheduled visit. Shift tables from baseline (baseline of cycle 5) for values outside the normal ranges will be presented as appropriate.

Listings will be produced for all laboratory parameters.

### 8.8.4 Vital signs

Observed values and changes from baseline (baseline of cycle 1) for vital sign measurements (temperature, blood pressure, pulse rate, and respiratory rate) will be summarized by treatment group and overall for each scheduled visit. Change from baseline (baseline of cycle 5) vital sign data will be presented by treatment group and overall from cycle 5 for each scheduled visit.

A listing will be produced for all vital signs.

### 8.8.5 Physical examinations

All physical examination data and abnormalities (Normal, Abnormal-NCS, Abnormal-CS and Not Examined) will be summarized by treatment group and overall for each scheduled visit (including pre-treatment and post-treatment results).

A listing will be produced for all physical examination data.

### 8.8.6 12-lead Electrocardiograms

Observed values and changes from baseline (baseline of cycle 1) of continuous 12-lead ECG measurements (Heart Rate (beats/min), QRS Duration (msec), PR Interval (msec), QT Interval (msec), QTc Interval Unspecified (msec)) will be summarized by treatment group and overall for each scheduled protocol assessment visit.

Shift tables from baseline (baseline of cycle 5) to end of treatment visit of normal vs. abnormal (NCS, CS) assessments will be provided by treatment group and overall.

Clinically notable abnormalities with thresholds of:

QTcF value > 450 msec, > 480 msec and > 500 msec, change of from baseline > 30 msec, > 60 msec and > 90 msec;

PR interval<120 msec or >210 msec, QRS complex >110 msec

will be summarized by treatment group at each scheduled visit using descriptive statistics.

A listing will be produced for all ECG measurements.

### 8.8.7 Other safety assessments

#### 8.8.7.1 Pharmacokinetics

The analysis of the PK will be described in a separate analysis plan if needed..

#### 8.8.7.2 Weight and BSA

Observed values and changes from baseline (baseline of cycle 1) for weight and BSA will be summarized by treatment group and overall for each scheduled visit. Change from baseline (baseline of cycle 5) data will be summarized by treatment group and overall from cycle 5 for each scheduled visit.

A listing will be produced for all weight, BSA and BMI.

#### 8.8.7.3 ECOG

All ECOG data will be summarized by treatment group and overall for each scheduled visit (including pre-treatment and post-treatment results). Shift table from baseline (baseline of cycle 5) to each post-baseline scheduled visit will be provided by treatment group and overall.

A listing will be produced for all ECOG data.

#### 8.8.7.4 Pregnancy

Pregnancy test results will be listed.

#### 8.8.7.5 LVEF

Visit values and changes from baseline (baseline of cycle 1) for LVEF will be summarized by treatment group and overall for each scheduled protocol assessment visit. Change from baseline (baseline of cycle 5) data will be summarized by treatment group and overall from cycle 5 for each scheduled visit.

In addition, LVEF quantitative values will be classified into the following 4 categories:

Hyperdynamic: LVEF greater than 70%

Normal: LVEF from 50% to 70% with midpoint 60%

Mild dysfunction = LVEF from 40% to 49% with midpoint 45%

Moderate dysfunction = LVEF from 30% to 39% with midpoint 35%

Severe dysfunction = LVEF less than 30%

Shift tables from baseline (baseline of cycle 5) to end of treatment visit of LVEF quantitative values will be provided by treatment group and overall.

A listing will be produced for all LVEF.

### 8.9 Interim analysis

Not applicable.

# 9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

Not applicable.

# 10 REFERENCES

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7. FDA Statistical Review and Evaluation of CT-P13. Available at https://www.accessdata fda.gov/drugsatfda_docs/nda/2016/125544Orig1s000StatR.pdf. Accessed Mar 07, 2018

# 11 APPENDICES

## Appendix 1 Dose Modification Guidelines

### Trastuzumab Dose Modifications

| Trastuzumab Dose Adjustment Guidelines | |
|---|---|
| **Infusion Reaction** | • Mild or moderate: decrease rate of infusion<br>• Dyspnea or clinically significant hypotension: interrupt infusion, administer appropriate medical therapy, which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, or oxygen; monitor until complete resolution<br>• Severe or life-threatening: consider permanent discontinuation |
| **Decline of LVEF**<br><br>**Asymptomatic absolute decline ⩾ 16% from baseline**<br><br>**OR**<br><br>**Absolute decline ⩾10% from baseline and below the institutional limit of normal** | • Initiate monthly monitoring of LVEF and consider cardiac support<br>• Hold trastuzumab for at least 4 weeks<br>• Dosing may resume if within 4-8 weeks the LVEF returns to normal limits and the absolute decrease from baseline is ⩽15%.<br>• Permanently discontinue trastuzumab<br>  • If persistent (>8 weeks) LVEF decline<br>  • If suspension of trastuzumab dosing on more than 3 occasions for cardiomyopathy |
| **Symptomatic cardiac failure** | • Hold trastuzumab, monitor LVEF and seek cardiology input |

### Epirubicin Dose Modifications

Epirubicin hydrochloride injection dosage adjustments for hematologic and non-hematologic toxicities within a cycle of treatment, is based on nadir platelet counts <50,000/mm$^3$, absolute neutrophil counts (ANC) <250/mm$^3$, neutropenic fever, or Grades 3/4 nonhematologic toxicity. Reduce Epirubicin hydrochloride injection Day 1 dose in subsequent cycles to 75% of the Day 1 dose given in the current cycle. Delay Day 1 chemotherapy in subsequent courses of treatment until platelet counts are ≥100,000/mm$^3$, ANC ≥1500/mm$^3$, and nonhematologic toxicities have recovered to ≤ Grade 1.

**Paclitaxel Dose Modifications**

| Paclitaxel Dose Adjustment Guidelines | |
|---|---|
| **Grade 2 neuropathy** | • Reduce paclitaxel by 1 dose level.<br>• Trastuzumab should continue at the same dose level. |
| **Grade ≥3 neuropathy** | • Hold paclitaxel until event resolves or returns to baseline.<br>• Decrease paclitaxel dose by 1 dose level.<br>• Trastuzumab should continue at the same dose level. |
| **Grade 3 or 4 acute hypersensitivity despite adequate premedication** | • Discontinue paclitaxel and consider trastuzumab monotherapy. |
| **ANC <1000/mm$^3$ (1.0 × 10$^9$/L), or platelet <75,000/mm$^3$ (75 × 10$^9$/L) on day of scheduled paclitaxel treatment** | • Hold paclitaxel until ANC ⩾1000/mm$^3$ (1.0 × 10$^9$/L), and platelet ⩾75,000/mm$^3$ (75 × 10$^9$/L).<br>• Consider treatment with growth factor (eg, G-CSF) according to local guidelines.<br>• If event reoccurs, reduce paclitaxel by 1 dose level.<br>• Trastuzumab should continue at the same dose level. |
| **Grade 4 neutropenia lasting ⩾7 days**<br>Grade 4 febrile neutropenia<br>Grade 3 or 4 documented infection with neutropenia (ANC <1000/mm$^3$ [1.0 × 10$^9$/L]) | • Hold paclitaxel until ANC ⩾1000/mm$^3$ (1.0 × 10$^9$/L).<br>• Reduce paclitaxel by 1 dose level.<br>• Consider treatment with growth factor (eg, G-CSF) according to local guidelines.<br>• Trastuzumab should continue at the same dose level.<br>• If event reoccurs, reduce paclitaxel to the next lower dose level or discontinue paclitaxel at the investigator's discretion. |
| **Grade 4 thrombocytopenia** | • Hold paclitaxel until platelet ⩾75,000/mm$^3$ (75 × 10$^9$/L).<br>• Reduce paclitaxel by 1 dose level.<br>• Trastuzumab should continue at the same dose level.<br>• If the event reoccurs, reduce paclitaxel to the next lower dose level or discontinue paclitaxel at the investigator's discretion. |

| Paclitaxel Dose Adjustment Guidelines | |
|---|---|
| **For potential cases of drug-induced liver injury** | • Hold paclitaxel.<br>• Contact the Sponsor immediately to discuss next steps, including evaluation of alternative causes.<br>• This must be reported as an SAE. Refer to the AE section for additional information on potential drug-induced liver injury. |
| **Other Grade 3 or 4 non-hematologic toxicity including nausea and/or vomiting despite optimal medical therapy, and fatigue/asthenia lasting more than 3 days** | • Hold paclitaxel until recovery to Grade 1 or baseline.<br>• Paclitaxel dose adjustment and/or paclitaxel or trastuzumab discontinuation should be performed according to the investigator's medical judgment. |

**Cyclophosphamide Dose Modifications**

| **Cyclophosphamide Dose Adjustment Guidelines** | | | |
|---|---|---|---|
| **Hematological Toxicity** | Delay 1 week if neutrophils <1.0 x $10^9$/L and/or platelets <100 x $10^9$/L. 20% dose reduction should be considered if myelosuppression results in delay of subsequent courses | | |
| **Renal Impairment** | **Creatinine Clearance (mL/min)** | | **Cyclophosphamide Dose** |
| | > 21 | | 100% |
| | 10 to 20 | | 75% |
| | < 10 | | 50% |
| **Hepatic Impairment** | **Bilirubin** | **ALT/ Alkaline Phosphatase** | **Cyclophosphamide Dose** |
| | 1.5 to 3 x ULN | 2.5 to 5 x ULN | 100% |
| | 3 to 5 x ULN | 5 to 10 x ULN | 100% |
| | .> 5 x ULN | .> 10 x ULN | Consider dose reduction / use alternative regimen* |
| | * Cyclophosphamide is not recommended in patients if bilirubin > 1.5 x ULN or AST/ALT >2 to 3xULN, but exposure to active metabolites may not be increased and therefore a dose reduction may not be necessary. Consultant decision. | | |
| **NCI Common Toxicity Criteria** | **Toxicity** | **Definition** | **Dose Adjustment** |
| | Febrile neutropenia | ANC < 0.5 x $10^9$/L plus fever requiring IV antibiotics +/- hospitalization | 20% reduction |
| | Other toxicities | Grade III/IV toxicity (except alopecia) | Continue with 20% dose reduction of suspected causative agent(s) provided toxicity has resolved to Grade I or less. If further toxicity occurs, an additional reduction may be made after discussion with consultant |
| | Defer treatment for any grade III/IV non-haematological toxicity (excluding alopecia).<br>If a delay of more than 3 weeks is required for recovery, or more than 2 dose reductions are necessary, the patient should discontinue treatment. | | |

## Appendix 2 RECIST version 1.1 Guidelines

Adapted from *Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 2009;45(2):228–47.*

**CATEGORIZING LESIONS AT BASELINE**

**Measurable Lesions**

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm), measured in the axial plane. If the slice thickness is greater than 5 mm (including any inter-slice gap), the longest diameter must be at least twice the slice thickness.
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray, only if the tumor is clearly outlined by well-aerated lung.
- Malignant lymph nodes with a short axis (defined as the largest measurement perpendicular to the longest diameter of the lesion) 15 mm or greater when assessed by CT or MRI.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other lesions.

**Non-measurable disease**

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, superficial lesions, and abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

**Normal sites**

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

**Tumor Assessments**

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within the window of time specified in Table 3.3.1 prior to treatment and all disease must be documented appropriately. If the baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

The determination of whether lesions are measurable is performed only at baseline. "Measurable" at baseline means eligible for selection as target lesions, and thus for quantitative assessment throughout the study. Once selected as a target lesion, a lesion remains target throughout the study.

**Target lesions**

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to look for partial response at later assessments.

- If 2 target lesions coalesce the longest diameter measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

**Non-target disease**

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

**OBJECTIVE RESPONSE STATUS AT EACH EVALUATION**

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If not, subsequent objective statuses may be indeterminate.

**Target disease**

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy) with a minimum absolute increase of 5 mm.
- Objective Response Rate (ORR) defined as the percentage of subjects having Complete or Partial Response at EOT/ET, based on radiographic assessments of the tumor.
- Indeterminate. Progression has not been documented, and
    - one or more target lesions have not been assessed,
    - or assessment methods used were inconsistent with those used at baseline and impaired assessment,
    - or one or more target lesions cannot be measured accurately (e.g. poorly visible unless due to being too small to measure),
    - or one or more target lesions were excised or irradiated and have not reappeared or increased.

**Non-target disease**

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be ‘normal’ in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of stable disease (SD) or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

**New Lesions**

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

**Supplemental Investigations**

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

**Subjective progression**

Subjects requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment eCRFs. This should be indicated on the EOT/ET eCRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

**Table 1. Objective Response Status at each Evaluation**

| Target Lesions | Non-target Disease | New Lesions | Objective status |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | Indeterminate or Missing | No | PR |
| PR | Non-CR/Non-PD, Indeterminate, or Missing | No | PR |
| SD | Non-CR/Non-PD, Indeterminate, or Missing | No | Stable |
| Indeterminate or Missing | Non-PD | No | Indeterminate |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |