CLINICAL STUDY PROTOCOL

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

NCT03556358

Document Date: 30 November 2017

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

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

Protocol No.: TX05-03 Amendment 1	IND No.: 116582
EudraCT No.: 2017-004190-13	
Test Product:	TX05 (Trastuzumab)
Indication:	Breast Cancer
Sponsor:	Tanvex Biologics Corp.
Development Phase:	III
Sponsor Signatory:	[redacted]
Date of the Protocol:	30 November 2017
Version of the Protocol:	Final

2 SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

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

PROTOCOL NUMBER: TX05-03

[redacted]

CLINICAL RESEARCH ORGANIZATION SIGNATURE PAGE

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

PROTOCOL NUMBER: TX05-03

[redacted]

Signature

INVESTIGATOR SIGNATURE PAGE

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

PROTOCOL NUMBER: TX05-03

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Name and Job Title	Date *(day/month/year)*

Signature

3 GENERAL INFORMATION

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

Protocol No.:	TX05-03
Date of the Protocol:	30 November 2017
Number of Amendment(s):	1
Sponsor:	Tanvex Biologics Corp. 33F, No. 99, Sec 1 Xintai 5th Street Xizhi District New Taipei City 221 Taiwan
Clinical Research Organization:	[redacted]
Sponsor Signatory:	[redacted]

4 STUDY SYNOPSIS

Name of Sponsor/Company: Tanvex Biologics Corp.	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Product: TX05		
Name of Active Ingredient: Trastuzumab	**Volume:** **Page:**	

Title of Study:
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

Study Center(s):
It is planned that approximately 209 centers will be initiated for this study in 19 countries.

Publication(s):
None.

Planned Study Period:	**Development Phase:**
October 2017 to August 2019	Phase III

Objectives:

Primary Objective:

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 human epidermal growth factor receptor positive (HER2+) invasive early breast cancer (EBC).

Secondary Objective:

To compare objective response rate (ORR) between the 2 treatment arms; immunogenicity, safety, and tolerability will also be assessed.

Methodology:

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 24), 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 single agent adjuvant treatment with trastuzumab (Herceptin or TX05) for up to 10 treatment cycles.

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

- Intravenous (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.

Tumor status will be evaluated at Screening. Radiographic assessments (computed tomography [CT] scan of chest or magnetic resonance imaging of chest [only if CT scan cannot be performed] and bilateral mammography or ultrasound) obtained per the subject's standard of care (SOC) prior to randomization do not need to be repeated and are acceptable to use as baseline evaluations, as long as the following criteria are met:

- Obtained within 6 weeks before randomization.
- Were performed using the method requirements outlined in Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (see Appendix 4), and
- Are the same technique/modality that will be used to follow identified lesions throughout the trial and at the End of Treatment/Early Termination (EOT/ET) Visit.

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Subjects will attend study visits every 3 weeks (± 3 days). Study procedures include physical examination, vital signs, weight, Eastern Cooperative Oncology Group (ECOG) performance status, clinical laboratory tests, adverse events (AEs), and concomitant medication.

Cardiac safety will be assessed at Screening, Cycle 5 (Week 12) (prior to administration of study drug), and at the EOT/ET Visit using 12-lead electrocardiogram (ECG) and echocardiography or multi-gated acquisition (MUGA) scan to evaluate the left ventricular ejection fraction (LVEF).

Samples for the evaluation of anti-drug antibodies (ADA), including neutralizing antibodies (Nab) will be obtained prior to initiation of infusion at Cycle 5 (Week 12), prior to infusion at Cycle 7 (Week 18), and the EOT/ET Visit.

Pharmacokinetic samples for assessment of trough serum concentration (C_{trough}) will be taken from 100 subjects in each treatment arm (200 total) 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.

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 (Week 24). Subjects will undergo a definitive surgical resection of their primary tumor, as part of their SOC, i.e., lumpectomy or mastectomy with sentinel node (SN) biopsy or axillary lymph node dissection (ALND). Surgical resection will be performed within 3 to 7 weeks from the 1st day of the last cycle/last dose of study drug.

The primary efficacy endpoint, pCR, is the proportion of subjects in each treatment arm who achieve pCR (ypT0/Tis ypN0). Pathology of the tumor sample and pathologic response will be assessed locally and reviewed centrally by a qualified pathologist. Assessments will be compliant with FDA guidance and sites will be provided with training for site pathologists. Surgeons will follow the standard local process for performing the biopsy.

Number of Subjects:

It is planned that 800 subjects will be enrolled to ensure completion of 740 subjects.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Signed written informed consent.
2. Females ≥ 18 years of age.
3. Histologically confirmed HER2 overexpressing invasive primary operable Stage II/IIIa breast cancer by American Joint Committee on Cancer 7th Edition staging criteria. Tumor tissue sample must be available for central analysis.
4. Planned surgical resection of breast tumor (lumpectomy or mastectomy, and SN biopsy or ALND).
5. Planned neoadjuvant chemotherapy.
6. HER2 overexpression as assessed by:
   - Gene amplification by fluorescent in-situ hybridization (FISH), chromogenic in-situ hybridization (CISH), or dual in-situ hybridization (DISH) (as defined by the manufacturer's kit instruction); OR
   - Overexpression by immunohistochemistry (IHC) categorized as IHC 3+; OR
   - Overexpression by immunohistochemistry categorized as IHC2+ with FISH, CISH, or DISH confirmation.

   Central review will be performed retrospectively for subjects who were determined to be HER2 positive by use of either an approved assay listed in Appendix 1 or two different analytical test methods that were not considered Sponsor approved. The results from non-approved IHC and in-situ hybridization analytical tests must be unequivocal (i.e., IHC result must be categorized as IHC3+).

   If a subject's tumor HER2 status cannot be determined by using an approved assay (see Appendix 1) or two different HER2 assays performed locally, a tissue sample can be sent to the central laboratory early in

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Screening for evaluation; results of the assessment will be returned to the investigator for inclusion in subjects' source documents.

7. Ipsilateral, measurable tumor longest diameter > 2 cm.
8. Known estrogen receptor (ER) and progesterone receptor (PR) hormone status prior to randomization. If ER/PR status is not available locally, testing may be performed by central laboratory during Screening.
9. ECOG performance status of 0 or 1.
10. Adequate bone marrow, hepatic, and renal functions as evidenced by the following:
    - Absolute neutrophils count ≥ 1,500/µL
    - Hemoglobin ≥ 9 g/dL
    - Platelet count ≥ 100,000/µL
    - Creatinine clearance ≥ 40 mL/min
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
    - Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) and alanine aminotransferase (serum glutamic pyruvic transaminase) ≤ 2.5 x ULN
    - Alkaline phosphatase ≤ 5 x ULN
11. LVEF ≥ 50% or within the normal level of the institution, as assessed by echocardiography or MUGA scan.
12. Able to comply with the study protocol.
13. Female subjects of childbearing potential must have a negative serum pregnancy test within 1 week of first administration of study drug and agree to use effective contraception (hormonal contraceptive, intrauterine device, diaphragm with spermicide, or condom with spermicide) throughout the study period and for 6 months after last administration of study drug.

Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Participation in any interventional clinical study or having taken any investigational therapy during the 2 month period immediately preceding administration of the first dose of study drug.
2. Bilateral breast cancer.
3. Inflammatory breast cancer.
4. Metastases.
5. Previous chemotherapy, biologic therapy, radiation, or surgery for any active malignancy, including breast cancer.
6. Subjects with one or more of the following conditions:
    - Cardiac insufficiency (New York Heart Association III or IV); myocardial infarction, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident, unstable angina pectoris, uncontrolled arrhythmia, or pulmonary embolus within the previous 12 months prior to the first administration of study drug.
    - Clinically significant active infection.
    - Poorly controlled diabetes mellitus.
    - Uncontrolled hypertension (blood pressure > 150/100 mmHg despite optimal medical therapy).
    - Major surgery, significant traumatic injury, or radiation therapy within 4 weeks of first administration of study drug.
    - Grade 3 hemorrhage within 4 weeks of first administration of study drug.
7. Pre-existing clinically significant (≥ Grade 2) peripheral neuropathy.
8. History of malignancy within the last 5 years, except adequately excised squamous or basal cell carcinoma of the skin, cervical carcinoma *in situ*, and superficial bladder cancer.
9. Severe dyspnea at rest requiring supplementary oxygen therapy.

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10. Known positive status for human immunodeficiency virus.
11. Known acute or chronic-active infection with hepatitis B surface antigen or hepatitis C virus.
12. History or presence of a medical condition or disease that in the investigator's opinion would place the subject at an unacceptable risk for study participation.
13. Lactating or pregnant female.
14. Women of childbearing potential who do not consent to use highly effective methods of birth control (e.g. true abstinence [periodic abstinence {e.g. calendar ovulation, symptothermal, post-ovulation methods} and withdrawal are not acceptable methods of contraception], sterilization, or other non-hormonal forms of contraception) during treatment and for at least 6 months after the last administration of study drug. Subjects must agree to not breast-feed while receiving study drug.
15. Subject has known sensitivity to any of the products to be administered during the study, including mammalian cell derived drug products, trastuzumab, murine proteins, or to any of the excipients.
16. Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range despite optimal medical therapy.
17. Subject likely to not be available to complete all protocol required study visits or procedures.

Test Product, Dose, and Mode of Administration:

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

Treatment with TX05 will be preceded by IV epirubicin, 75 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles.

Reference Therapy, Dose, and Duration of Administration:

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

Treatment with Herceptin will be preceded by IV epirubicin, 75 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles.

Duration of Treatment:

The study will consist of a Screening period (Days -28 to 0) and a double-blind neoadjuvant treatment period (Week 0 [Day 1] to Week 21), an EOT/ET Visit at Week 24, followed by surgery (3 to 7 weeks from the 1st day of the last cycle/last dose of study drug).

Criteria for Evaluation:

Efficacy Endpoints:

Primary efficacy endpoint: the proportion of subjects in each treatment arm who, based on the central pathological review, 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.

Secondary efficacy endpoint: ORR, according to RECIST version 1.1 (see Appendix 4), as assessed by the investigator.

Immunogenicity Assessments:

- Incidence of ADA.
- Incidence of Nab.

Safety Assessments:

- Treatment-emergent AE (TEAE) and serious AE (SAE).
- Death
- Clinical laboratory parameters

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- Vital signs
- 12-Lead ECG cardiac ejection fraction
- Physical examination

Statistical Methods:

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.

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. The mITT population will be used for sensitivity analysis of the primary efficacy endpoint and for primary analysis of secondary efficacy endpoints.

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

- mITT population.
- No major protocol deviations that impact the efficacy endpoints.
- An adequate tumor sample by definitive surgical resection of their primary tumor.

The PP population will be used as the primary analysis for the primary efficacy endpoint.

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

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 θ_1 is the proportion of pCR for subjects randomized to TX05 group, θ_2 is the proportion of pCR for subjects randomized to Herceptin. Equivalence will be concluded if the 95% confidence interval of the risk ratio is completely contained within the pre-defined interval [0.755, 1.325].

No interim analysis is planned.

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Appendix 2 ECOG Performance Status

Appendix 3 Estimated Creatinine Clearance Using the Cockcroft-Gault formula

Appendix 4 RECIST version 1.1 Guidelines

Appendix 5 Dose Modification Guidelines

6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
ALND	Axillary lymph node dissection
ANC	Absolute neutrophil counts
$AUC_{0-\infty}$	Area under the plasma concentration-time curve 0 to infinity
AUC_{0-24}	Area under the plasma concentration-time curve 0 to 24 hours
AUC_{0-t}	Area under the plasma concentration-time curve 0 to last measured concentration
BSA	Body surface area
CI	Confidence interval
CISH	Chromogenic in-situ hybridization
C_{max}	Maximum concentration
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough serum concentration
DISH	Dual in-situ hybridization
EBC	Early breast cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOT	End of Treatment
ER	Estrogen receptor
ET	Early termination
EU	European Union
FDA	Food and Drug Administration
FISH	Fluorescent in-situ hybridization
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
IEC	Independent ethics committee
IgG1	Immunoglobulin G1

IHC	Immunohistochemistry
IRB	Institutional review board
IV	Intravenous
IWRS	Interactive web response system
LLOQ	Lower limit of quantitation
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition
Nab	Neutralizing antibodies
NCCN	National Comprehensive Cancer Network
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
SAE	Serious adverse event
SAP	Statistical analysis plan
SN	Sentinel node
SOC	Standard of care
SOP	Standard operating procedure
SST	Serum separator tube
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic
T_{max}	Time to maximum concentration
TNFα	Tumor necrosis factor alpha
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor

7 INTRODUCTION

7.1 Background

Human epidermal growth factor receptor (HER2) belongs to a family of growth factor tyrosine kinase receptors which include endothelial growth factor receptor, HER1, HER3 and HER4 receptors[1]. By forming hetero-homo-dimers with members of the family, they play a critical role in mediating cell growth, differentiation, and survival. The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the HER1. HER2 protein overexpression is observed in 25%–30% of primary breast cancers.

In a subset of breast cancers, a high level of HER2 is detected that is 10 to 100 times greater than that found in the normal breast epithelium[2,3]. Even a moderate overexpression leads to a constitutively activated HER2 receptor by associating with itself, thus enhancing its tyrosine kinase activities. Tyrosine kinase activity promotes an increased proliferation rate, resistance to tumor necrosis factor alpha (TNFα), decreased expression of adhesion molecules, and increased vascular endothelial growth factor (VEGF) secretion[3,4].

Trastuzumab (Herceptin®) is a humanized monoclonal antibody that recognizes an extracellular epitope (amino acids 529-627), a region very close to the transmembrane region of HER2[5]. A major mechanism by which trastuzumab exerts its activity is through binding to HER2. Herceptin-bound HER2 will not hetero/homodimerize, which in turn, will down-regulate the receptor activity and subsequently lead to the inhibition of the signal transduction pathway[6]. Trastuzumab has been shown, both *in vitro* and in animals to inhibit the growth of human tumor cells that overexpress HER2[7,8,9]. In *in vitro* studies, a treatment of trastuzumab reduces cellular resistance to TNFα[10], restores adhesion molecules[11], and reduces VEGF production[12]. In addition to the inhibition of receptor-mediated functions, trastuzumab has a strong antibody-dependent cellular cytotoxicity (ADCC) against HER2 overexpressing cells. This component of trastuzumab-dependent ADCC is an important factor in the specificity of trastuzumab activity since HER2 overexpressing tumor cells would likely be preferentially targeted for ADCC rather than tissues with normal level of HER2[13,14].

Herceptin was approved for marketing in the United States (US) by the Food and Drug Administration (FDA) in 1998 and in the European Union (EU) in 2000. A comprehensive program of nonclinical pharmacology and toxicology studies were completed to support its safe clinical use. It is indicated for the treatment of HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in the FDA label and for HER2 positive metastatic breast cancer, HER2 positive early breast cancer (EBC) and HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction in the European Medicines Agency (EMA) label. A series of clinical studies, including pharmacokinetic (PK) and safety/efficacy studies support the approved indications, including the treatment of HER2-overexpressing breast cancer and the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Study results and adverse events (AEs) associated with the use of trastuzumab are described in the Herceptin package insert.

TX05 is being developed as a proposed biosimilar product to the approved trastuzumab (Herceptin). It is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to the extracellular domain of HER2 (ErbB2/HER2p185). TX05 is a highly purified protein that contains a 1328 amino acid humanized monoclonal IgG1 antibody. TX05 has an identical amino acid sequence and similar physicochemical and *in vitro* functional properties to trastuzumab.

7.2 Nonclinical Studies

7.2.1 Nonclinical Pharmacology

The Sponsor has performed a detailed analytical and functional characterization and comparison of TX05 and US-licensed Herceptin. Physicochemical characterization showed identical primary sequence, and similar physicochemical characteristics in terms of size, charge, glycan profiles and other parameters. *In vitro* biological characterization focused on the biological activities that are most relevant to the *in vivo* function of trastuzumab also showed a great degree of similarity between TX05 and Herceptin. Importantly, recent characterization data support that certain manufacturing improvements that were implemented after the initial clinical PK study of TX05 have further improved the similarity of TX05 to Herceptin with respect to levels of afucosylated glycans and associated biologic activity (FcγRIIIA binding and ADCC activity) (Section 7.3.1).

7.2.2 Pharmacokinetics

The PK of TX05 in comparison to US-licensed Herceptin have been evaluated in Sprague-Dawley rats and in Cynomolgus monkeys.

In Sprague-Dawley rats, TX05, Herceptin (25 mg/kg), or vehicle control was administered by a single intravenous (IV) bolus injection into the tail vein. Plasma concentrations of TX05 and Herceptin were quantifiable over the 14-day sampling period. All pre-dose concentrations and control samples concentrations were below the lower limit of quantitation (LLOQ) (0.100 µg/mL). As expected for IV bolus dosing, peak TX05 or Herceptin concentrations were reached at the first sampling timepoint of 10 minutes for both dose groups. Concentration profiles for both compounds followed a slow decline resulting in an indeterminate terminal elimination phase, consequently terminal half-life ($t_{1/2}$), volume of distribution and clearance were not reported. TX05 and Herceptin exposure were similar with a calculated TX05-to-Herceptin ratio of 1.08 for area under the plasma concentration-time curve 0 to 24 hours (AUC_{0-24}). There were no anti-drug antibodies (ADA)-related effects on the overall exposure of TX05 or Herceptin in the dosed groups given that all samples from the dosed groups were either screened or confirmed negative for ADA.

In female Cynomolgus monkeys (4 per group), 2 to 5 years of age, TX05 or Herceptin (25 mg/kg) was administered by a single IV bolus injection. PK parameters were generated from TX05 and Herceptin individual concentrations in plasma from Day 1. Plasma

concentrations of TX05 and Herceptin were quantifiable over the 28-day sampling period. All pre-dose concentrations were below the LLOQ. Peak concentrations were observed at 2.5 hours after the start of infusion for TX05 and at 2 hours after the start of infusion for Herceptin. The exposure between TX05 and Herceptin was considered to be similar, and the differences in the toxicokinetic (TK) parameters were within the standard deviations calculated.

No distribution studies of TX05 have been performed. However, in the European summary basis of approval for Herceptin, it was noted that the distribution and fate of radiolabeled (^{125}I) trastuzumab were compared with those of similarly labelled human IgG1 in tumor-bearing beige-nude athymic mice (Herceptin European public assessment report). Through tissue and blood analysis, and whole-blood autoradiography, it was shown that the disposition of the specific (trastuzumab) and non-specific IgG1 antibodies were similar in blood and non-tumor tissues. However uptake of radioactivity was localized in tumor tissue for ^{125}I-labeled trastuzumab and not for IgG1, and was shown to be saturable. Peak tumor uptake occurred 24 to 48 hours after administration and ranged from 22 to 66% dose/g of tissue.

7.2.3 Toxicology

A single dose comparative study with a single administration of TX05 and US-licensed Herceptin assessing PK, immunogenicity and systemic tolerability has been completed in Sprague-Dawley rats. Dose selection for the toxicology study was based upon consideration of the clinically relevant dose with the formulated material and providing toxicology data for comparison to US-licensed Herceptin. TX05, US-licensed Herceptin (25 mg/kg) or vehicle control were administered to the appropriate animals by IV (slow bolus) injection to the tail vein once on Day 1. Evaluations included in-life procedures (mortality, morbidity, clinical observation, body weight, and food consumption), laboratory evaluations, evaluation of ADA and complete necropsy evaluation of toxicology groups at termination.

All animals survived to scheduled necropsy. There were no related TX05 or Herceptin-related clinical observations during the study. All animals were normal throughout the study period. One Herceptin-dosed TK animal was noted with labored breathing, pale ear, and red periorbital skin on Day 1 after the 10-minute post-dose blood collection. These clinical signs were attributed to the animal struggling during the sample collection and were considered stress-related.

There was no detection of anti-TX05 or anti-Herceptin antibodies during the study. There were no changes in any parameters considered related to either TX05 or Herceptin administration, including in-life, clinical pathology, gross pathology, organ weights, and histopathology assessments.

7.2.4 Summary and Nonclinical Safety Assessment

Physicochemical characterization of TX05 as well as the side-by-side comparison with Herceptin, has shown identical primary sequence of the 2 proteins, and similar physicochemical characteristics in terms of size, charge and glycan profiles. The *in vitro*

pharmacology studies demonstrated the biosimilarity of TX05 to US-licensed Herceptin, with respect to several key biologic activities, including binding to the target receptor and inhibition of growth of HER2 expressing cells.

In vivo studies further support the biosimilarity of TX05 and Herceptin by demonstration of similarity in PK of TX05 and Herceptin in Sprague Dawley rats by similarity of exposure following a single dose of 25 mg/kg of TX05 or Herceptin, with a calculated TX05/Herceptin ratio of 1.08 for AUC_{0-24}; and in Cynomolgus monkeys, by exposure and clearance following a single dose of 25 mg/kg of TX05 or Herceptin, with a ratio between AUC_{0-24} of TX05 to Herceptin of 1.21.

Good tolerability of TX05 and Herceptin in Sprague-Dawley rats was demonstrated following a single dose of 25 mg/kg of TX05 or Herceptin, with no changes in any parameters related to TX05 or Herceptin, including laboratory parameters, in-life, clinical pathology, gross pathology, organ weights and histopathology. Similarly, good tolerability of a single dose of 25 mg/kg of TX05 or Herceptin was seen in Cynomolgus monkeys, with no clinical signs associated with either test article.

7.3 Clinical Studies

7.3.1 Pharmacokinetics

A Phase 1 PK study of TX05 and Herceptin in 70 healthy adult male subjects has been completed and demonstrated PK similarity of TX05 in comparison to the reference product, US-licensed Herceptin. Secondary study objectives were to compare the safety and tolerability of TX05 and the reference product and to assess the incidence of ADA. The primary endpoint of this PK study was the area under the plasma concentration-time curve 0 to infinity ($AUC_{0-\infty}$). PK similarity was claimed if the 90% confidence interval (CI) of the ratio of means of the log-transformed $AUC0_{-\infty}$ was entirely within the limits of (80.00%, 125.00%). Other PK endpoints included area under the plasma concentration-time curve 0 to last measured concentration (AUC_{0-t}) and maximum concentration (C_{max}).

Values of time to maximum concentration (T_{max}) ranged between 1.50 and 6.00 hours for both TX05 and Herceptin. Mean $AUC_{0-t/\infty}$ values were 96.53% and 98.55% for the test and reference formulation, respectively. It is considered that the sampling schedule covered the concentration-time curve long enough to provide a reliable estimate of the extent of exposure.

The PK and statistical results indicate that the test/reference ratio of means of log-transformed $AUC_{0-\infty}$ was 93.32% (90% CI 86.79 - 100.34%), for log-transformed AUC_{0-t} was 91.20% (90% CI 84.58 - 98.34%), and for log-transformed C_{max} was 96.12% (90% CI 90.68 - 101.88%). The point estimates and their 90% CIs were all contained within the range of 80.00% to 125.00% demonstrating the PK similarity of TX05 to US-licensed Herceptin.

As noted above, some manufacturing improvements were introduced for TX05 following this initial PK study. As the pre-change TX05 and Herceptin were shown to be PK equivalent in the initial PK study despite some minor differences, it is not anticipated that the improvements in post-change TX05 (Section 7.2.1), which have made it even more similar to Herceptin, would negatively impact the PK or safety profile similarity demonstrated in the

completed study. Additionally, a reduction in the level of Man5 in the post-change TX05, which could theoretically slightly reduce its clearance, may be expected to bring the AUC ratio of post-change TX05 and Herceptin even closer to 1. Therefore, post-change TX05 is expected to show a very similar PK to Herceptin as well as to the pre-change TX05.

7.3.2 Safety

In the PK study, both drugs were generally safe and well tolerated by study subjects. There were no discernible patterns in treatment-emergent AEs (TEAEs), laboratory, or electrocardiogram (ECG) parameters, and no treatment-emergent serious AEs (SAEs) were reported over the course of the study. Subjects in both treatment groups experienced TEAEs with a low frequency, of which, the most common were headache, upper respiratory tract infection and nasal congestion. Other TEAEs included nausea, drug screen positive, myalgia, and vomiting.

The severity of all TEAEs was mild to moderate. No severe or life-threatening TEAEs were reported in this study. The TEAEs reported as possibly, probably, or definitely related to study drug in both treatment groups were generally consistent with those previously reported to be associated with Herceptin (Herceptin package insert). Thirteen TEAEs were considered definitely related to study drug, including chills, injection site extravasation, neutrophil count decrease, nausea, headache, muscular weakness, myalgia, and ocular hyperemia. These TEAEs were reported by 3 subjects in TX05 group and 4 subjects in Herceptin group. All these TEAEs resolved by the end of the study. One subject was discontinued from the study following observation of chills, headache, and muscle weakness following initiation of a Herceptin infusion.

The assessment of anti-trastuzumab antibody at different timepoints revealed positive screen assay results in both Herceptin and TX05 groups prior to and/or after drug exposure. Following specificity assay/final results, only one subject in the TX05 group tested positive for anti-trastuzumab antibody at baseline; post-dose values were negative. No other subject tested positive for anti-trastuzumab antibody following the confirmatory assays in this study.

Further details are provided in the Investigator Brochure.

7.4 Rationale

TX05 is being developed as a potential biosimilar to Herceptin. A biosimilar medicine is a medicine that is similar to a biological medicine that has already been authorized (the biological reference medicine). Biosimilarity between the biosimilar and the biological reference medicine has to be established in a stepwise approach at all levels: quality, nonclinical, and clinical. The demonstration of biosimilarity is based on the concept of totality of the evidence, in which all structural, functional, nonclinical, and clinical data are evaluated to show high similarity to the reference product. As part of this stepwise approach, a clinical human study must be conducted in a sensitive and homogeneous subject population to demonstrate similar efficacy and safety compared to the reference product.

The studies detailed above in Section 7.2 and 7.3 have demonstrated similarity between TX05 and the reference product, Herceptin, and as well as the systemic tolerability of TX05.

The results from these studies, as well as comparability studies of TX05 before and following manufacturing improvements, were considered to be sufficient to support further clinical development of TX05.

A randomized, double-blind, parallel group, trial in subjects with HER2 positive EBC will be conducted to demonstrate that TX05 has similar efficacy, safety, and immunogenicity to Herceptin. Subjects who complete this study may be eligible to enroll in a separate (extension) protocol designed to further assess and characterize the safety and efficacy of TX05 and Herceptin as single agents.

This study will be conducted in compliance with the protocol and with the International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP).

8 STUDY OBJECTIVES

8.1 Primary Objective

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.

8.2 Secondary Objective

To compare objective response rate (ORR) between the 2 arms; immunogenicity, safety, and tolerability will also be assessed.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

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 10 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.

Tumor status will be evaluated at Screening. Radiographic assessments (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) obtained per the subject's standard of care (SOC) prior to randomization do not need to be repeated and are acceptable to use as baseline evaluations, as long as the following criteria are met:

- Obtained within 6 weeks before randomization.
- Were performed using the method requirements outlined in Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (see Appendix 4), and
- Are the same technique/modality that will be used to follow identified lesions throughout the trial and at the End of Treatment/Early Termination (EOT/ET) Visit.

Subjects will attend study visits every 3 weeks (± 3 days). Study procedures include physical examination, vital signs, weight, Eastern Cooperative Oncology Group (ECOG) performance status, clinical laboratory tests, AEs, and concomitant medication.

Cardiac safety will be assessed at Screening, Cycle 5 (Week 12) (prior to administration of study drug), and at the EOT/ET Visit using 12-lead ECG and echocardiography or multi-gated acquisition (MUGA) scan to evaluate the left ventricular ejection fraction (LVEF).

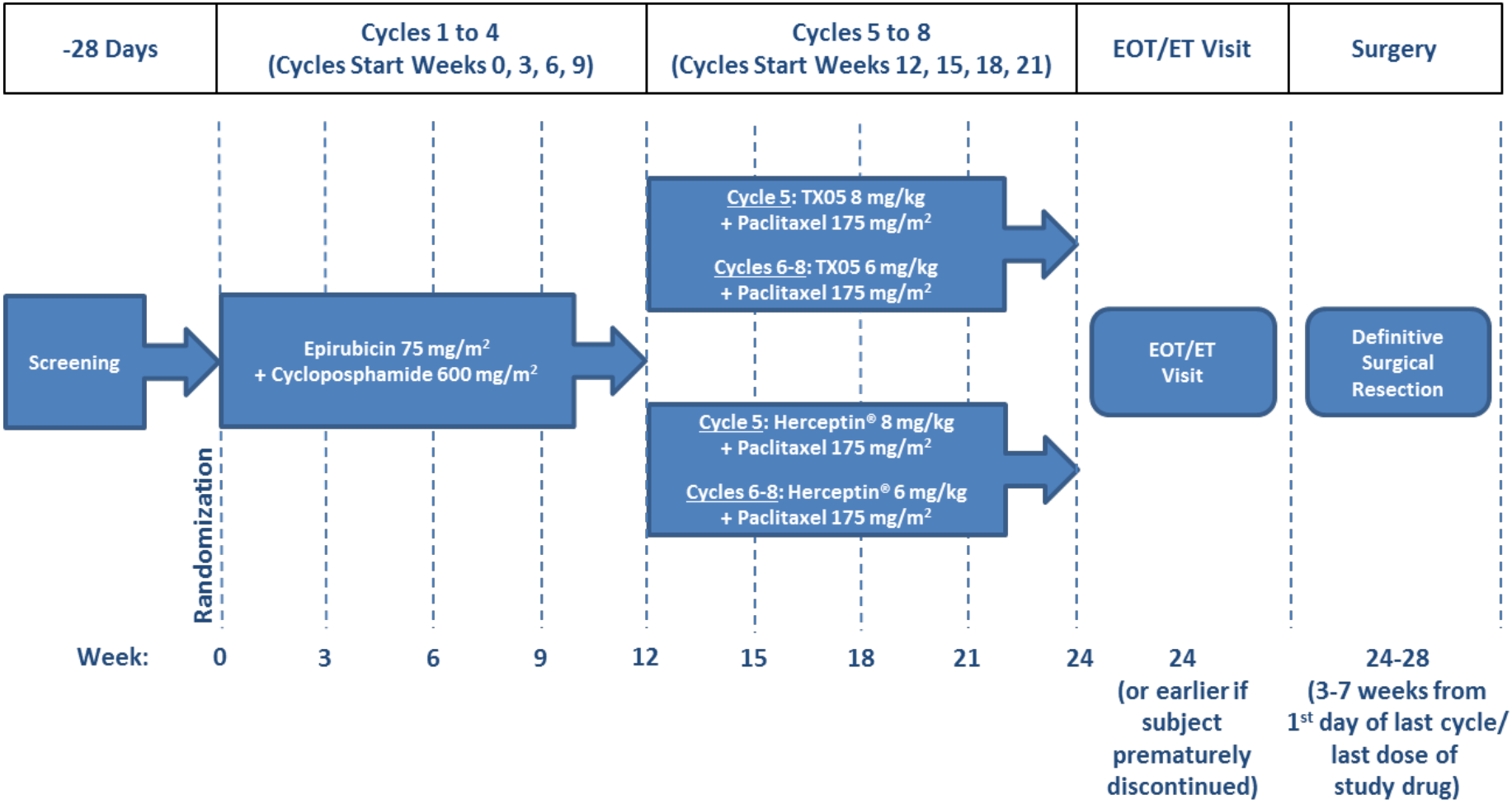
Samples for the evaluation of ADA, including neutralizing antibodies (Nab) will be obtained prior to initiation of infusion at Cycle 5 (Week 12), prior to infusion at Cycle 7 (Week 18), and the EOT/ET Visit.

Pharmacokinetic samples for assessment of trough serum concentration (C_{trough}) will be taken from 100 subjects in each treatment arm (200 total) 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.

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 (Week 24 or earlier if subject prematurely discontinued). Subjects will undergo a definitive surgical resection of their primary tumor, as part of their SOC, i.e., lumpectomy or mastectomy with sentinel node (SN) biopsy or axillary lymph node dissection (ALND). Surgical resection will be performed within 3 to 7 weeks from the 1st day of the last cycle/last dose of study drug.

The primary efficacy endpoint, pCR, is the proportion of subjects in each treatment arm who achieve pCR (ypT0/Tis ypN0). Pathology of the tumor sample and pathologic response will be assessed locally and reviewed centrally by a qualified pathologist. Assessments will be compliant with FDA guidance[15] and sites will be provided with training for site pathologists, providing detailed instructions for the pathologists' awareness. Surgeons will follow the standard local process for performing the biopsy. Full instructions for the preparation, handling, and shipping of the pathology samples will be included in the central laboratory manual.

Figure 9–1 Study Design Flow Diagram



9.1.1 Schedule of Assessments

The schedule of assessments is presented in Table 9–1.

Table 9–1 Schedule of 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 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	
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, as part of their standard of care (SOC), 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 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, as part of their SOC, i.e., lumpectomy or mastectomy with sentinel node (SN) biopsy or axillary lymph node dissection (ALND). Surgical resection will be performed within 3 to 7 weeks from the 1st day of the last cycle/last dose of study drug. Pathology of the tumor sample and pathologic response will be assessed locally and reviewed centrally by a qualified pathologist.

The schedule of blood samples that will be drawn for each subject is presented in Table 9–2.

Table 9–2 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, following AEs, or as clinically indicated.

9.1.2 Study Assessments

9.1.2.1 Screening Period -28 days

Subjects are to undergo a Screening Visit 28 days prior to the planned first day of study treatment. Screening assessments are as follows:

- Obtain written informed consent
- Record demographic information
- Record medical and surgical history
- Perform physical examination (including height at Screening only)
- Record weight and body surface area (BSA)
- Record vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Perform pregnancy test (for subjects of childbearing potential) (within 1 week of first administration of study drug)
- Assess ECOG performance status
- Assess eligibility criteria
- Confirm histologically invasive breast cancer
- Confirm HER2 status based on local laboratory test performed at the time of diagnosis. If HER2 status is unknown it must be taken using approved test (see Appendix 1) or two different analytical test methods that were not considered Sponsor approved. Central laboratory testing may be used to determine HER2 status if test is not available locally. Confirm tumor tissue sample is available for central laboratory.
- Perform estrogen receptor (ER) and progesterone receptor (PR) testing if not already known and documented
- Perform clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Perform viral disease screen (Hepatitis B surface antigen [HBsAg], hepatitis C virus [HCV], and/or Human Immunodeficiency Virus [HIV] only in countries where regulations mandate testing or if warranted by known subject history)
- Perform 12-lead ECG
- Assess LVEF (echocardiography or MUGA)
- Perform tumor assessment

9.1.2.2 Randomization

Randomization will occur after the Screening Visit and prior to the treatment period.

9.1.2.3 Treatment Period: Epirubicin + Cyclophosphamide: Cycle 1 (Week 0) to Cycle 4 (Week 9)

Cycle 1 (Week 0)

- Record weight and BSA
- Record vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Perform pregnancy test (for subjects of childbearing potential)
- Assess ECOG performance status
- Perform clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Study drug administration
- Record AEs
- Assess subject compliance
- Record concomitant medications

Cycle 2 (Week 3), Cycle 3 (Week 6), and Cycle 4 (Week 9)

- Record weight and BSA
- Record vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Perform pregnancy test (for subjects of childbearing potential)
- Assess ECOG performance status
- Perform clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Study drug administration
- Record AEs
- Assess subject compliance
- Record concomitant medications

9.1.2.4 Treatment Period: TX05/Herceptin + Paclitaxel: Cycle 5 (Week 12) to Cycle 8 (Week 21)

Cycle 5 (Week 12)

- Record weight and BSA
- Record vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Perform pregnancy test (for subjects of childbearing potential)
- Assess ECOG performance status
- Perform clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Perform 12-lead ECG
- Assess LVEF (echocardiography or MUGA)
- Perform immunogenicity sampling
- Perform PK sampling (prior to initiation of infusion in 100 subjects per treatment arm)
- Study drug administration
- Record AEs
- Assess subject compliance
- Record concomitant medications

Cycle 6 (Week 15), Cycle 7 (Week 18), and Cycle 8 (Week 21)

- Record weight and BSA
- Record vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Perform pregnancy test (for subjects of childbearing potential)
- Assess ECOG performance status
- Perform clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Perform immunogenicity sampling (Cycle 7 [Week 18] only)
- Perform PK sampling (prior to initiation of infusion in 100 subjects per treatment arm)
- Study drug administration
- Record AEs
- Assess subject compliance
- Record concomitant medications

9.1.2.5 End of Treatment/Early Termination Visit (Week 24) - Prior to Surgery

- Perform physical examination
- Record vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Assess ECOG performance status
- Perform clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Perform 12-lead ECG
- Assess LVEF (echocardiography or MUGA)
- Perform tumor assessment
- Perform immunogenicity sampling
- Perform PK sampling (in 100 subjects per treatment arm)
- Record AEs
- Record concomitant medications

9.1.2.6 Surgery (Week 24 to 28 - 3 to 7 weeks from the 1st day of the last cycle/last dose of study drug)

- Definitive surgical resection/obtain tumor sample

9.2 Discussion of Study Design

The hypothesis tested in this clinical study is that TX05 has sufficient similarity of PK, safety, efficacy, and immunogenicity to Herceptin to support market approval and availability to subjects for whom trastuzumab treatment is indicated.

To develop a biosimilar, the PK, efficacy, and safety profiles of the proposed biosimilar must be similar to the marketed product. In order to support global development of TX05 as a biosimilar, one comparator arm is included in this study. The comparator to be used in this clinical study is EU-licensed Herceptin.

As noted above, TX05 has been shown to be similar to US-licensed Herceptin with respect to *in vitro* physicochemical and functional characterization, and *in vivo* PK and safety profile in animals and in healthy human subjects. The PK and safety/tolerability profile similarity of EU and US-licensed Herceptin has been demonstrated in published PK studies of trastuzumab biosimilar candidates[16,17,18]. Due to the demonstrated PK similarity of TX05 and US-licensed Herceptin, it is considered that these studies indirectly support the anticipated PK similarity of TX05 with EU-licensed Herceptin, and thus the use of EU-licensed Herceptin as a comparator for the proposed study. This will be formally assessed in a 3-way PK bridging study that will be conducted in parallel to the study described herein in order to demonstrate the PK and safety similarities between TX05, US and EU-licensed Herceptin.

Trastuzumab given every 3 weeks (8 mg/kg loading dose, 6 mg/kg maintenance dose) is per the US Herceptin label for EBC[19]. The US Herceptin label does not include an indication in the neoadjuvant breast cancer setting, however, it is widely used in clinical practice and neoadjuvant trastuzumab treatment is recommended by the National Comprehensive Cancer Network (NCCN) guideline on breast cancer (Version 2 2017)[20].

For this intended biosimilar, TX05, HER2 positive EBC potentially amenable to surgery provides a sensitive and uniform population of subjects. For this population of EBC, pathological complete response, pCR, following neoadjuvant treatment has been shown to correlate with progression-free survival and overall survival. There is precedence for use of and this endpoint in both the US and EU as the primary endpoint for biosimilar equivalence studies for trastuzumab.

The most frequently published pCR definition (absence of invasive neoplastic cells in the breast and lymph nodes) and FDA guidance to industry[15] will be used in this study consistent with previous studies investigating trastuzumab given concurrently with taxanes and anthracyclines in the neoadjuvant setting[21].

9.2.1 Risk/Benefit and Ethical Assessment

There is a substantial body of data related to the safety and efficacy of Herceptin in subjects with breast or gastric cancer (FDA and EMA Herceptin prescribing information). No studies of TX05 have been conducted in subjects with EBC. However, as mentioned, there is substantial nonclinical and clinical pharmacological and PK data showing the biosimilarity of TX05 to US-based Herceptin.

In general, the risks and discomforts anticipated to be associated with TX05 in subjects with breast cancer are those that are known for Herceptin and may include fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, shortness of breath, rash, neutropenia (low white blood cells), anemia (low red blood cells), and muscle aches. Serious side effects that have been documented with Herceptin include cardiomyopathy, serious infusion reactions, embryo-fetal toxicity, pulmonary toxicity, and exacerbation of chemotherapy-induced neutropenia as noted in the prescribing information for Herceptin. Please refer to Herceptin prescribing information for more detail. There may be additional risks or side effects that are related to TX05 and that are unknown at this time.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Signed written informed consent.
2. Females ≥ 18 years of age.
3. Histologically confirmed HER2 overexpressing invasive primary operable Stage II/IIIa breast cancer by American Joint Committee on Cancer 7th Edition staging criteria. Tumor tissue sample must be available for central analysis.
4. Planned surgical resection of breast tumor (lumpectomy or mastectomy, and SN biopsy or ALND).
5. Planned neoadjuvant chemotherapy.
6. HER2 overexpression as assessed by:
   - Gene amplification by fluorescent in-situ hybridization (FISH), chromogenic in-situ hybridization (CISH), or dual in-situ hybridization (DISH) (as defined by the manufacturer's kit instruction); OR
   - Overexpression by immunohistochemistry (IHC) categorized as IHC 3+; OR
   - Overexpression by immunohistochemistry categorized as IHC2+ with FISH, CISH, or DISH confirmation.

- Central review will be performed retrospectively for subjects who were determined to be HER2 positive by use of either an approved assay listed in Appendix 1 or two different analytical test methods that were not considered Sponsor approved. The results from non-approved IHC and in-situ hybridization analytical tests must be unequivocal (i.e., IHC result must be categorized as IHC3+).
- If a subject's tumor HER2 status cannot be determined by using an approved assay (see Appendix 1), or two different HER2 assays performed locally, a tissue sample can be sent to the central laboratory early in Screening for evaluation; results of the assessment will be returned to the investigator for inclusion in subjects' source documents.

7. Ipsilateral, measurable tumor longest diameter > 2 cm.
8. Known ER and PR hormone status prior to randomization. If ER/PR status is not available locally, testing may be performed by central laboratory during Screening.
9. ECOG performance status of 0 or 1 (see Appendix 2).
10. Adequate bone marrow, hepatic, and renal functions as evidenced by the following:
    - Absolute neutrophils count ≥ 1,500/µL
    - Hemoglobin ≥ 9 g/dL
    - Platelet count ≥ 100,000/µL

- Creatinine clearance ≥ 40 mL/min (see Appendix 3)
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) and alanine aminotransferase (serum glutamic pyruvic transaminase) ≤ 2.5 x ULN
- Alkaline phosphatases ≤ 5 x ULN

11. LVEF ≥ 50% or within the normal level of the institution, as assessed by echocardiography or MUGA scan.
12. Able to comply with the study protocol.
13. Female subjects of childbearing potential must have a negative serum pregnancy test within 1 week of first administration of study drug and agree to use effective contraception (hormonal contraceptive, intrauterine device, diaphragm with spermicide, or condom with spermicide) throughout the study period and for 6 months after last administration of study drug.

9.3.2 Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Participation in any interventional clinical study or having taken any investigational therapy during the 2 month period immediately preceding administration of the first dose of study drug.
2. Bilateral breast cancer.
3. Inflammatory breast cancer.
4. Metastases.
5. Previous chemotherapy, biologic therapy, radiation, or surgery for any active malignancy, including breast cancer.
6. Subjects with one or more of the following conditions:
   - Cardiac insufficiency (New York Heart Association III or IV); myocardial infarction, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident, unstable angina pectoris, uncontrolled arrhythmia, or pulmonary embolus within the previous 12 months prior to the first administration of study drug.
   - Clinically significant active infection.
   - Poorly controlled diabetes mellitus.
   - Uncontrolled hypertension (blood pressure > 150/100 mmHg despite optimal medical therapy).
   - Major surgery, significant traumatic injury, or radiation therapy within 4 weeks of first administration of study drug.
   - Grade 3 hemorrhage within 4 weeks of first administration of study drug.

7. Pre-existing clinically significant (≥ Grade 2) peripheral neuropathy.
8. History of malignancy within the last 5 years, except adequately excised squamous or basal cell carcinoma of the skin, cervical carcinoma *in situ*, and superficial bladder cancer.
9. Severe dyspnea at rest requiring supplementary oxygen therapy.
10. Known positive status for HIV.
11. Known acute or chronic-active infection with HBsAg or HCV.
12. History or presence of a medical condition or disease that in the investigator's opinion would place the subject at an unacceptable risk for study participation.
13. Lactating or pregnant female.
14. Women of childbearing potential who do not consent to use highly effective methods of birth control (e.g. true abstinence [periodic abstinence {e.g. calendar ovulation, symptothermal, post-ovulation methods} and withdrawal are not acceptable methods of contraception], sterilization, or other non-hormonal forms of contraception) during treatment and for at least 6 months after the last administration of study drug. Subjects must agree to not breast-feed while receiving study drug.
15. Subject has known sensitivity to any of the products to be administered during the study, including mammalian cell derived drug products, trastuzumab, murine proteins, or to any of the excipients.
16. Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range despite optimal medical therapy.
17. Subject likely to not be available to complete all protocol required study visits or procedures.

9.3.3 Withdrawal of Subjects

A subject may withdraw from the study at any time at her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons without compromising the subject’s medical care.

If a subject is off treatment for greater than 4 weeks due to any reason (for example toxicity, other AE/SAE, non-compliance, lost to follow-up) then she should be discontinued from study treatment. If possible (i.e. subject is not lost to follow-up) EOT procedures should be performed.

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

Subjects who withdraw from the study prior to the EOT/ET Visit should complete the procedures scheduled for that visit.

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, she may request destruction of any samples that have been taken and not yet tested, and the investigator must document this in the site study records.

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's medical record and electronic case report form (eCRF).

9.3.4 Lost to Follow-Up

A subject will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a subject fails to return to the site for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, she will be considered to be lost to follow-up.

9.3.5 Early Termination

This study may be terminated at any time by the Sponsor for any reason, including if serious side-effects should occur, if the investigator does not adhere to the protocol or if, in the Sponsor's judgment, there are no further benefits to be achieved from the study. In this event, the Sponsor will inform the study investigators, institutions, and all regulatory authorities.

9.3.6 Missed Dose

If the subject has missed a dose of TX05/Herceptin by 1 week or less, then the usual maintenance dose (6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be administered 21 days later according to three-weekly schedule.

If the subject has missed a dose of TX05/Herceptin by more than 1 week, a re-loading dose of TX05/Herceptin should be administered over approximately 90 minutes (8 mg/kg) as soon as

possible. Subsequent TX05/Herceptin maintenance doses (6 mg/kg) should be administered 21 days later according to the three-weekly schedule.

10 TREATMENT OF SUBJECTS

10.1 Identity of Study Treatment(s)

10.1.1 Administration of Study Treatment(s)

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 bacteriostatic 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).

Specific instructions on dose preparation and administration are provided in the separate dosage and administration instructions.

10.2 Treatment Regimen Adjustments

Chemotherapy regimens should be administered according to the local label.

Dose modification guidelines are provided in Appendix 5.

In the event of toxicity attributed to trastuzumab, treatment should be either temporarily or permanently discontinued, as below. Following a temporary discontinuation, treatment may

resume with the administration of a loading dose of trastuzumab in accordance with local SOC.

- Decrease the rate of infusion for mild or moderate infusion reactions.
- Interrupt the infusion in subjects with dyspnea or clinically significant hypotension.
- Discontinue the infusion for severe or life-threatening infusion reactions.

10.3 Study Treatment Packaging and Labeling

The labels of the study drug will be in the local language and comply with the legal requirements of each country. All blank spaces should be completed by site staff prior to dispensing to subjects.

10.3.1 Storage

The study drug may be prepared up to 24 hours prior to dose administration, where it is stored refrigerated (2ºC to 8ºC/36ºF to 46ºF) or up to 8 hours where it is stored below 30ºC (86ºF), and protected from light. Study drug should be removed from refrigerator and allowed to acclimate to room temperature over approximately 15 minutes prior to infusion.

10.4 Blinding and Randomization of Study Treatment(s)

Both randomization and blinding techniques will be used in this study to minimize bias. This is a double-blinded study and so 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. 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.

10.4.1 Procedure for Breaking the Randomization Code

Blinding should only be broken in emergency situations for reasons of individual subject safety when knowledge of the study drug assignment is required for medical management. Whenever possible, the investigator or sub-investigator can consult with a member of the study team prior to breaking the blind; however, should a situation arise where unblinding is required, the investigator at that site may perform immediate unblinding without the need for communication with the Sponsor. At all other times, treatment and randomization information will be kept confidential and will not be released to the investigator/site staff until the conclusion of the study.

If the blind for a subject has been broken, the reason must be fully documented in source documents and entered on the eCRF. Any AE or SAE associated with breaking the blind must be recorded and reported as specified in this protocol.

10.5 Subject Compliance

Study treatment will be administered under the supervision of the investigator/site staff. Compliance will be monitored by site staff by using the source documents and the eCRFs. The site study pharmacist is responsible for drug preparation, the maintenance of accurate and complete dispensing and accountability forms showing the receipt and dispensation of study drug. The pharmacist will also be responsible for performing accountability and reconciliation of the study drug, and documentation of background therapy administered, including tracking the number of vials used and manufacturer's lot numbers.

10.6 Study Treatment Accountability

Each vial dispensed must be recorded in the Study Drug Accountability Log.

Records shall be maintained of the delivery of study treatment(s) to the study center(s), the inventory at the study center(s), the use of each subject and the return to the Sponsor.

These records shall include dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the study drug and to the study subjects.

The investigator shall be responsible for ensuring that the records adequately document that the subjects were provided the doses specified in the protocol and that all study drug received from the Sponsor is reconciled. All randomization codes must be returned to the Sponsor at the end of the study.

10.7 Concomitant Therapy

Concomitant medications administered for any reason must be locally-approved and doses used and regimens that are considered SOC for the treated indication.

Medications and (non-drug treatments) will be monitored continuously by the investigator. Treatment for co-morbidities, disease signs and symptoms and TEAEs should be provided as necessary in the judgment of the investigator. Supportive care may include premedication with antiemetics to limit treatment-related nausea and vomiting. Subjects may receive prophylaxis of treatment-induced diarrhea. Anti-inflammatory or narcotic analgesics may be offered as needed.

Prophylactic use of hematopoietic growth factors to support neutrophil or platelet counts according to local SOC is permitted during this study. Subjects who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and subjects may start either drug during the study at the discretion of the investigator. Subjects with neutropenic fever or infection should be treated promptly and may receive therapeutic colony-stimulating factors if appropriate. Packed red blood cell and platelet transfusions may be administered as clinically indicated.

All concomitant medications and treatments should be recorded in the subject's source documents and entered into the eCRF, available during study monitor visits, and included in SAE reports.

Surgery during study participation to manage breast cancer lesions other than definitive surgery for the targeted tumor lesion post neoadjuvant therapy is discouraged unless

medically necessary in the judgment of the investigator. In this case, the subject will be discontinued from the study prior to the surgical procedure. In such cases, the EOT/ET Visit should be completed.

No other investigational drug may be used during treatment on this protocol, and concurrent participation in another clinical study is not allowed.

11 ASSESSMENTS

11.1 Endpoints

11.1.1 Primary Endpoint:

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.

11.1.2 Secondary Endpoint:

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 4), as assessed by the investigator.

11.1.3 Immunogenicity Assessments:

- Incidence of ADA.
- Incidence of Nab.

11.2 Disease Assessment

CT scan of chest or MRI of chest (only if CT scan cannot be performed) and bilateral mammography or ultrasound of the breast is required at Screening for all subjects. 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 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 RECIST version 1.1 (see Appendix 4).
3. The same imaging technique should be used throughout the study for the subject.
4. Appropriate documentation indicating that these radiographic tumor assessments were performed as SOC is available in the subject's source notes.

The CT scans should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. Depending on the adequacy for evaluation of disease, a combination of CT without contrast should most often be used. CT without contrast is preferred for evaluation of lesions in lung parenchyma. MRI is not adequate for evaluation of lung parenchyma but should also be performed to evaluate of all other aspects of the chest.

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.

11.3 Definitive Surgical Resection

Subjects will undergo a definitive surgical resection of their primary tumor, as part of their SOC, i.e., lumpectomy or mastectomy with SN biopsy or ALND. Surgical resection will be performed within 3 to 7 weeks from the 1st day of the last cycle/last dose of study drug. Pathology of the tumor sample and pathologic response will be assessed locally and reviewed centrally by a qualified pathologist, and data will be documented by the investigator in the source documentation and in the eCRF. Sites will follow standard operating procedures (SOPs) for collection and handling of pathology specimens to be compliant with FDA guidance[15]. Sites will be provided with training for surgeons and site pathologists. Surgeons will follow the instructions provided to ensure localization of the tumor bed, postoperative specimen radiographs to verify excision and use of colored sutures or other approaches to orient the specimen. Full instructions for the preparation, handling, and shipping of the pathology samples will be included in the central laboratory manual.

Pathological assessment requires adequate sampling of the correct area of the breast and should follow the guidelines provided, including:

- Correlate area to sample with clinical and imaging findings (pretreatment tumor size and location).
- Identify clip, if present/tumor bed.
- Document the (largest) cross section(s) of pretreatment area of involvement with a map of the tissue blocks (a minimum of 1 block prepared per centimeter of pretreatment tumor size, or at least 10 blocks in total, whichever is greater, with 3 to 5 mm slices). Areas of concern identified by either the radiologist's interpretation of the specimen radiograph(s) or the pathologist's assessment of the gross specimen(s) should be subjected to more extensive sectioning. Given that tumors may shrink concentrically or irregularly, subjects with no evidence of residual disease identified on initial evaluation should have additional blocks examined to ensure that no residual disease has been overlooked, and in particular, that no positive margins have been missed that may be surgically improved. All surgically removed lymph nodes must be entirely submitted for histologic evaluation, sectioned at 2-mm intervals.

The percentage of subjects in each treatment group who have pCR will be determined, using the resulting data from the assessments of the tumors following surgery after treatment completion and according to FDA guidance[15].

11.4 Objective Response Rate

Radiographic assessments of the tumor will be performed within 6 weeks prior to randomization and at the EOT/ET Visit. An ORR status will be determined at the EOT/ET Visit using the RECIST version 1.1 guidelines (see Appendix 4).

11.5 Tumor HER2, Progesterone Receptor and Estrogen Receptor Testing

Tumor HER2 status and the PR and ER status will be assessed at Screening. Tumor tissue blocks or slides will be assessed by the local laboratory as outlined in the Laboratory Manual. Tissue samples for HER2 status and eligibility must be available and sent to the central laboratory for concordance testing.

Central review will be performed retrospectively for subjects who were determined to be HER2 positive by use of either an approved assay listed in Appendix 1 or two different analytical test methods that were not considered Sponsor approved.

If a subject's tumor HER2 status cannot be determined by using an approved assay (see Appendix 1 [or two different HER2 assays performed locally]), due to lack of site availability or ability to perform such testing, a tissue sample can be sent to the central laboratory early in Screening for potential eligibility evaluation; results of the assessment will be returned to the investigator for inclusion in subjects' source documents.

Concordance testing results will not be shared with the sites or filed in site files. If sites use local testing for inclusion of a subject and the central lab HER2 result is discrepant, the subject will not be included in the PP population at the time of analysis.

If PR and ER hormone status can't be assessed locally at Screening, testing may be performed by the central laboratory. These results will be sent back to the site and should be filed in the subject's medical record.

11.6 Echocardiogram/MUGA

Assessment of LVEF using an echocardiogram or MUGA scan will be performed at Screening and prior to dosing at Cycle 5 (Week 12) and the EOT/ET Visit. The modality used for individual subjects should be consistent throughout the study.

11.7 Pharmacokinetic Sampling

Pharmacokinetic samples will be taken from 100 subjects in each treatment arm (200 total) 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. Sites will be notified which subjects will be included in this PK sampling. PK sampling is not to be done unless the subject is selected and the same subjects will be used for all PK assessments timepoints. The PK samples will be taken for assessment of C_{trough}.

Whole blood samples (7 mL) will be collected (see Table 9–2) to provide approximately 3 mL of serum for drug concentration measurement at each timepoint. Blood samples will be collected into appropriately labeled glass tubes containing no additive (a silicone coated plastic tube is acceptable if non-additive glass red top tube is not available). A serum separator tube (SST) should not be used.

Blood samples will be allowed to clot at room temperature for at least 20 minutes for a complete clot. The clotted samples will be placed into an ice bath for approximately 10 minutes prior to the centrifugation. Serum will be separated from the whole blood within approximately 40 minutes of collection. The specimen should be centrifuged at 1500 x g for

approximately 10 minutes in an ambient centrifuge (a refrigerated centrifuge is acceptable if available) to harvest the serum. After centrifugation, the upper serum layer is carefully transferred with a disposable pipette and split into 2 labeled screw capped plastic storage tubes (each with approximately 1.5 mL of serum, one for PK analysis and the other one for back-up shipment/PK analysis, respectively). The same plastic storage tubes will be frozen and thawed for each assay. The sample should be re-centrifuged immediately if red blood cells are inadvertently drawn into the serum. Serum samples will be frozen in an upright position at approximately -70°C (-20°C is acceptable if -70°C is not available at the site) within 90 minutes of sample collection.

11.8 Immunogenicity Sampling

Serum samples for detection of ADA and Nab will be collected prior to initiation of infusion of study drug at Cycle 5 (Week 12), prior to infusion of study drug 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.

Whole blood samples (7 mL) will be collected (see Table 9–2) to provide approximately 3 mL of serum for drug concentration measurement at each timepoint. Blood samples will be collected into appropriately labeled glass tubes containing no additive (a silicone coated plastic tube is acceptable if non-additive glass red top tube is not available) at times specified above. An SST should not be used.

Blood samples will be allowed to clot at room temperature for at least 20 minutes for a complete clot. The clotted samples will be placed into an ice bath for approximately 10 minutes prior to the centrifugation. Serum will be separated from the whole blood within approximately 40 minutes of collection. The specimen should be centrifuged at 1500 x g for approximately 10 minutes in an ambient centrifuge (a refrigerated centrifuge is acceptable if available) to harvest the serum. After centrifugation, the upper serum layer is carefully transferred with a disposable pipette and split into 2 labeled screw capped plastic storage tubes (each with approximately 1.5 mL of serum for ADA and Nab analysis respectively). The same plastic storage tubes will be frozen and thawed for each assay. The sample should be re-centrifuged immediately if red blood cells are inadvertently drawn into the serum. Serum samples will be frozen in an upright position at approximately -70°C (-20°C is acceptable if -70°C is not available at the site) within 90 minutes of sample collection. The shipment address and assay laboratory contact information will be provided to the investigator prior to or during the initiation of the study.

11.9 Laboratory Assessments

Hematology and clinical chemistry tests will include the parameters presented in Table 11–1.

Hematology and clinical chemistry samples will be drawn at the timepoints described in Table 9–1. A total of 4 mL for hematology samples and 4.5 mL for clinical chemistry samples will be drawn (see Table 9–2). Additional blood tests may be performed per SOC, at the investigator's discretion for the purpose of planning treatment administration, dose modification, following AEs, or as clinically indicated.

Table 11–1 Hematology and Clinical Chemistry Assessments

Hematology	Clinical Chemistry
Hemoglobin	Alanine Aminotransferase
Platelets	Aspartate Aminotransferase
White Blood Cells	Alkaline Phosphatase
Absolute Neutrophil Count	Sodium
	Potassium
	Total Calcium
	Total Bilirubin
	Blood Urea Nitrogen or Urea
	Creatinine
	Albumin

Urinalysis, including pH, erythrocyte, leukocyte, glucose, and protein will be conducted at the same visits at which blood laboratory tests are performed.

Viral disease screening: HBsAg, HbcAb, HCV, and HIV testing to demonstrate eligibility is required only in countries where regulations mandate testing or if warranted by known subject history.

All tests will be performed by local laboratories.

11.10 Electrocardiogram Assessments

12-lead ECGs will be performed at Screening, prior to dosing at Cycle 5 (Week 12), and at the EOT/ET Visit. 12-lead ECGs will be obtained after the subject has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the subject in the same physical position. A standardized ECG machine should be used, and the subject should be examined using the same machine throughout the study if possible.

An assessment of normal or abnormal will be recorded and if the ECG is considered abnormal, the abnormality will be documented on the eCRF. In cases where a clinical significant abnormality is found at baseline (Screening), this should be recorded in the subject's medical history. Should a clinically significant abnormality be reported during the treatment period, it will be recorded as an AE.

11.11 Physical Examination

Complete physical examinations will be conducted at Screening and at the EOT/ET Visit, including general appearance, skin, eyes, ear/nose/throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other body systems if applicable for describing the status of their health. All other evaluations will be at the discretion of the investigator.

Height will be recorded at Screening only. 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

collected from Day 1 of each cycle should be used to calculate the dosage of chemotherapy to be administered. BSA should be calculated using the DuBois formula as follows:

$BSA = 0.007184 \times (\text{weight [kg]}^{0.425} \times \text{height [m]}^{0.725})$

11.12 Vital Signs

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be performed at all timepoints. All tests will be obtained in the sitting position after the subject has rested for 10 minutes. The date and time of the assessment should be recorded on the subject's eCRF.

12 SAFETY MONITORING AND REPORTING

12.1 Adverse Events

12.1.1 Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The investigator is responsible for ensuring this.

Adverse Event

An AE is defined as any untoward medical occurrence in a subject, or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigation) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Event

An SAE is defined as, but is not limited to, one that:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse drug experience, when based on appropriate medical judgment, they may jeopardize the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.1.1.1 Recording of Adverse Events

For the purposes of this study, any detrimental change in the subject's condition, after signing the informed consent form and up to completion of the study should be considered an AE.

SAEs will be recorded from Screening, while AEs will be recorded from Day 1 (Week 0) of Cycle 1 of study treatment.

All ongoing AEs should be followed up for 30 days after the last administration of study drug, with the exception of any ongoing study drug-related AEs, which should be followed until resolution, unless in the investigator's opinion, the AE is unlikely to resolve due to the subject's underlying disease. Any new SAEs occurring up to 30 days after the last administration of study drug, or until enrollment in the extension study, should be reported according to Section 12.1.6.

At any time after the EOT/ET Visit, if an investigator learns of an SAE that can be reasonably related to study drug, he/she should promptly notify the Sponsor.

The investigator will assess the intensity of AEs based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.03:

- Mild (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)
- Moderate (minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living)
- Severe (hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living)
- Life-threatening (urgent intervention indicated)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 12.1.1.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

The investigator will use his/her clinical judgment to determine the degree of likelihood that the study product (TX05 or Herceptin) was responsible for the reported AE/SAE. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product, will be considered and investigated. The investigator should consult the Investigator's Brochure in the determination of his/her assessment.

The standard nomenclature for defining the causal relationship between an AE and the study product is listed in the following table (Table 12–1).

Table 12–1 Classification of AE Relationship to Investigational Product

Unrelated	No temporal association to study product. An alternate etiology has been established. The event does not follow the known pattern of response to study product. The event does not reappear or worsen with re-challenge.
Probably not related/remote	No temporal association to study product. Event could readily be produced by clinical state, environmental or other interventions. The event does not follow the known pattern of response to study product. The event does not reappear or worsen with re-challenge.
Possibly related	Reasonable temporal relationship to study product. The event is not readily produced by clinical state, environmental, or other interventions. The event follows a known pattern of response to the study product or as yet unknown pattern of response.
Probably related	There is a reasonable temporal association with the study product. The event is not readily produced by clinical state, environmental, or other interventions. The event follows a known pattern of response to the study product. The event decreases with de-challenge.
Definitely related	There is a reasonable temporal relationship to the study product. The event is not readily produced by clinical state, environmental, or other interventions. The event follows a known pattern of response to the study product. The event decreases with de-challenge and recurs with re-challenge.

For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study drug and the AE.

12.1.2 Abnormal Laboratory Values/Vital Signs/Electrocardiograms

Laboratory/vital signs/ECG abnormalities should be reported as AEs if any one of the following criteria is met:

- Any criterion for an SAE is fulfilled.
- The laboratory/vital signs abnormality causes the subject to discontinue from the study treatment.
- The laboratory/vital signs abnormality causes the subject to interrupt the study treatment.
- The laboratory/vital signs abnormality causes the subject to modify the dose of study treatment.

- The investigator believes that the abnormality should be reported as an AE.
- If an abnormal laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom should be reported as an AE and the associated laboratory result or vital sign should be considered additional information that must be collected on the relevant eCRF.

12.1.3 Deaths

Should a death occur within the study period or within 30 days after the last administration of study drug an AE form and an SAE form should be completed, detailing the AE that resulted in the death (NB, death is an outcome, not an event). The SAE must be reported within 24 hours of awareness of the event by any site staff or study team member. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

12.1.4 Overdose

Treatment of study drug overdose (chemotherapy and trastuzumab) is at the discretion of the investigator.

12.1.5 Pregnancy

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.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even after the subject has been withdrawn from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to the Sponsor on a pregnancy outcomes report form.

12.1.6 Reporting of Serious Adverse Events

Investigators and other site personnel must inform appropriate [redacted] representatives of any SAE that occurs (whether or not attributable to the study drug) in the course of the study within one day (i.e., immediately but no later than the end of the next business day) of when he or she becomes aware of it.

All SAE reports must be faxed to the following number within 24 hours:

[redacted] DRUG SAFETY (Pharmacovigilance Department)

Europe and Asia Pacific

[redacted]

E-mail: [redacted]

Americas

[redacted]

E-mail: [redacted]

The [redacted] representative will work with the investigator to compile all the necessary information and ensure that the appropriate Sponsor representative receives a report within one day (24 hours) for all fatal and life-threatening cases and within 5 days for all other SAEs.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to [redacted] within one day as described above. For a non-serious AE that becomes serious but which is not fatal or life-threatening a report should be received within 5 days.

The following variables will be recorded for each AE: verbatim/AE description, time and date for AE start and stop, maximum intensity, seriousness, causality rating, whether or not the AE caused the subject to discontinue, and the outcome.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF. The investigator is responsible for informing the independent ethics committee (IEC) of the SAE as per local requirements. The investigator should report to [redacted] who will forward the report to the appropriate Sponsor representative.

13 STATISTICAL EVALUATION

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained during the study. This document may reflect modification to the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

13.1 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[22,23,24,25,26] 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 13–1 Rates of pCSR from Neoadjuvant Herceptin Studies

Name	Trastuzumab + Chemotherapy (T + C)	Chemotherapy Alone (C)
NOAH (MO16432)[22,23]	(n =115) 46 (40.0%)	(n=116) 24 (20.7%)
Buzdar[24]	(n=23) 15 (65.2%)	(n=19) 5 (26.3%)
Pierga[25]	(n=62) 16 (25.8%)	(n=58) 11 (19.0%)
ABCSG-24[26]	(n=44) 17 (38.6%)	(n=49) 13 (26.5%)
Combined risk ratio of pCR[a] 95% CI (T+C:C)	1.755[b] [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 trastzumab + 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.

13.2 Analysis Populations

13.2.1 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. The mITT population will be used for sensitivity analysis of the primary efficacy endpoint and for primary analysis of secondary efficacy endpoints.

13.2.2 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.
- An adequate tumor sample by definitive surgical resection of their primary tumor.

The PP population will be used as the primary analysis for the primary efficacy endpoint.

13.2.3 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.

13.3 Statistical Methods

13.3.1 General Principles

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.

A SAP will be prepared and finalized before study data are unblinded.

The statistical analysis will be performed using the SAS version 9.4 or higher.

13.3.2 Missing Data

Partial dates of start or stop date of AEs will be imputed in an appropriately conservative way; detailed methods will be described in the SAP.

Other missing values will not be imputed, unless otherwise specified.

13.3.3 Demographic and Baseline Characteristics

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

13.3.4 Subject Disposition

The following will be summarized (overall and by treatment group where applicable):

- Subjects screened
- Subjects randomized
- Subjects treated
- Subjects receiving study drug (TX05 or Herceptin)
- Subjects in each analysis set
- Subjects completing the study/withdrawing early (including withdrawal reason)
- Subject allocation by site

13.3.5 Efficacy Analysis

13.3.5.1 Analysis of Primary Endpoint

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). Subjects who are included in the analysis population but do not have efficacy assessments will be assessed as non-responders in the mITT population.

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 θ_1 is the proportion of pCR for subjects randomized to TX05 group, θ_2 is the proportion of pCR for subjects randomized to Herceptin. Justification of equivalence margin [0.755, 1.325] is described in the Section 13.1.

Equivalence will be concluded if the 95% CI of the risk ratio is completely contained within the pre-defined interval [0.755, 1.325].

This endpoint will be analyzed with the PP population. Detailed analysis will be described in the SAP.

13.3.5.2 Analysis of Secondary Endpoint

Secondary endpoints include the following:

- 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 4), as assessed by the investigator.

Frequency and percentage of subjects who meet the pCR and ORR criteria will be reported. Risk Ratio and its 95% CI will be estimated. Analysis will be performed with the mITT population and sensitive analysis will be performed with the PP population. Detailed analysis will be described in the SAP.

13.3.6 Immunogenicity Assessment

Immunogenicity data (ADA and Nab) will be summarized and analyzed descriptively for each scheduled protocol assessment time-point.

13.3.7 Safety Analysis

The safety parameters will include the following:

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

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, graded according to CTCAE, by treatment group and overall. TEAEs observed during Cycle 1 to 4 and TEAEs observed from Day 1 of Cycle 5 will be summarized separately by treatment group. Drug related TEAEs and SAEs will be also summarized by treatment group.

Clinical safety laboratory data: clinical safety laboratory data will be presented by treatment group and overall. For each visit, the actual result and the change from baseline will be presented. Shift tables for values outside the normal ranges will be presented as appropriate.

Otherwise, safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. For continuous measurements (laboratory and vital signs data), change from baseline will be additionally summarized by treatment and visit. Subject listings will be produced for all safety parameters.

The safety analysis will be carried with the safety population and will be analyzed according to the treatment they actually received. Detailed analysis will be described in the SAP.

13.3.8 Interim Analysis

There will be no interim analysis.

14 DIRECT ACCESS TO SOURCE DATA/NOTES

The investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, IEC/institutional review board (IRB) review and regulatory inspection.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Conduct of the Study

The Sponsor or designee shall implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with FDA regulations (CFR, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

15.2 Study Monitoring

The study will be monitored to ensure that it is conducted and documented according to the protocol, GCP, and all applicable regulatory requirements. On site visits will be made at appropriate times during the period of the study. Monitors must have direct access to source documentation in order to check the consistency of the data recorded in the eCRFs.

The investigator shall permit the monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

16 ETHICS

16.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH GCP, and local requirements as applicable.

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non-evaluable.

The IEC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures (e.g., advertisements), written information to be provided to the subjects, Investigator's Brochure, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory Authority (Competent Authority) as applicable.

16.2 Written Informed Consent

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

The nature and purpose of the study shall be fully explained to each subject (or their legally responsible guardian).

Written informed consent must be obtained from each subject (or guardian) prior to any study procedures being performed. The investigator will keep the original signed copies of all consent forms in his/her files and will provide a duplicate copy to the subject.

The informed consent document used during the informed consent process must be in compliance with ICH GCP, local regulatory requirements, and legal requirements reviewed by the Sponsor or designee, approved by the IRB/IEC before use, and available for inspection. A copy of the letter indicating IEC/IRB approval must be provided to the Sponsor or designee prior to the study initiations.

17 DATA HANDLING AND RECORD KEEPING

17.1 Case Report Forms/Source Data Handling

Clinical data will be entered on eCRFs for transmission to the Sponsor or designee. Data on eCRFs transmitted via the web based data system must correspond to and be supported by source documentation maintained at the study center. All study forms and records transmitted to the Sponsor or designee must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by the Sponsor or designee. Access to the EDC system is available to authorized users via the study's internet website, where an assigned username and password are required for access. The EDC system is in compliance with applicable data protection guidelines and regulations. The eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

17.2 Retention of Essential Documents

All records relating to the conduct of this study are to be retained by the investigator according to ICH, local regulations, or as specified in the clinical study agreement, whichever is longer. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and given the opportunity to further store such records. The investigator will allow representatives of Sponsor or Sponsor's designee (and of the applicable regulatory authorities) to inspect all study records, eCRFs, and corresponding portions of the study subjects' office and/or hospital medical records at regular intervals across the study. These inspections are for the purpose of verifying the adherence to the protocol, the completeness and accuracy of the data being filled in the eCRF, and compliance with applicable regulations.

The Sponsor and the investigator agree that the study subject medical records will be maintained in a confidential manner. The clinical study report will not identify any subject by name.

18 FINANCING AND INSURANCE

Financial aspects of the study are addressed in a separate clinical study agreement. The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

19 PUBLICATION POLICY

The Sponsor shall retain the ownership of all data. When the study is complete the Sponsor shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings, or submission to regulatory authorities. All proposed publications based on this study must be subject to the Sponsor's approval requirements.

20 REFERENCE LIST

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21 APPENDICES

Appendix 1 Approved HER2 Assays

HER2 results based on 1 of the following commercial kit assays are acceptable (for the purposes of study entry). Of note, additional HER2 assays approved by the FDA not listed below are also considered acceptable for the purposes of study entry.

IHC Approved Assay	FISH Approved Assay	CISH Approved Assay	DISH Approved Assay
HercepTest™ (Dako)	Pathvysion HER2 DNA Probe Kit (Abbott Molecular)	SPOT-Light® HER2 CISH™ Kit (Invitrogen Corporation)	INFORM HER2 Dual ISH DNA Probe Cocktail Assay (Ventana)
Pathway™ Her2 (Ventana)[a]	INFORM HER2/neu Probe (Ventana)	HER2 CISH PharmDx™ Kit (Dako)	
Bond™ Oracle™ HER2 IHC System (Leica Biosystems)	Dakocytomation HER2 FISH PharmDx™ Kit (Dako)		
PATHWAY HER2/neu (Ventana)[b]			

a. PATHWAY™ Her2 (clone CB11) is a mouse monoclonal antibody intended for laboratory use for the semi-quantitative detection of c-erbB-2 antigen in sections of formalin fixed, paraffin embedded normal and neoplastic tissue on a Ventana automated immunohistochemistry slide staining device.

b. PATHWAY HER-2/neu (clone 4B5) is rabbit monoclonal antibody intended for the semi-quantitative detection of HER2 antigent in sections of formalin-fixed, paraffin-embedded normal and neoplastic tissue. Created to run on a Ventana automated immunohistochemistry slide staining device, it is indicated as an aid in the assessment of breast cancer subjects for whom Herceptin treatment is considered.

Appendix 2 ECOG Performance Status

Grade	ECOG Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work or office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Appendix 3 Estimated Creatinine Clearance Using the Cockcroft-Gault formula

C_{Cr}={((140–age) x weight)/(72 x S_{Cr})}x 0.85 (if female)

Where C_{Cr} = creatinine clearance and S_{Cr} = serum creatinine (in mg/dL).

Appendix 4 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 9–1 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

Appendix 5 Dose Modification Guidelines

Trastuzumab Dose Modifications

Trastuzumab Dose Adjustment Guidelines	
Infusion Reaction	• Mild or moderate: decrease rate of infusion • Dyspnea or clinically significant hypotension: interrupt infusion, administer appropriate medical therapy, which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, or oxygen; monitor until complete resolution • Severe or life-threatening: consider permanent discontinuation

Decline of LVEF
 	
Asymptomatic absolute decline ≥16% from baseline
 	
OR
 	
Absolute decline ≥10% from baseline and below the institutional limit of normal
	• Initiate monthly monitoring of LVEF and consider cardiac support
	• Hold trastuzumab for at least 4 weeks
	• Dosing may resume if within 4-8 weeks the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%.
	• Permanently discontinue trastuzumab
	  • If persistent (>8 weeks) LVEF decline
	  • 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. • Trastuzumab should continue at the same dose level.
Grade ≥3 neuropathy	• Hold paclitaxel until event resolves or returns to baseline. • Decrease paclitaxel dose by 1 dose level. • 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). • Consider treatment with growth factor (eg, G-CSF) according to local guidelines. • If event reoccurs, reduce paclitaxel by 1 dose level. • Trastuzumab should continue at the same dose level.
Grade 4 neutropenia lasting ≥7 days Grade 4 febrile neutropenia 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). • Reduce paclitaxel by 1 dose level. • Consider treatment with growth factor (eg, G-CSF) according to local guidelines. • Trastuzumab should continue at the same dose level. • 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). • Reduce paclitaxel by 1 dose level. • Trastuzumab should continue at the same dose level. • If the event reoccurs, reduce paclitaxel to the next lower dose level or discontinue paclitaxel at the investigator's discretion.
For potential cases of drug-induced liver injury	• Hold paclitaxel. • Contact the Sponsor immediately to discuss next steps, including evaluation of alternative causes. • 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. • 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). 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.		