CLINICAL STUDY PROTOCOL

A double-blinded extension study to provide adjuvant treatment with single agent Herceptin® or TX05 and assess continued safety and immunogenicity in subjects with HER2-positive early breast cancer following neoadjuvant treatment and surgical resection in Protocol TX05-03

NCT04109391

Document Date: 13 December 2018

1 TITLE PAGE

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Protocol No.: TX05-03E	IND No.: 116582
EudraCT No.: 2018-000236-97	
Test Product:	TX05 (Trastuzumab)
Indication:	Breast Cancer
Sponsor:	Tanvex Biologics Corp.
Development Phase:	III
Sponsor Signatory:	[redacted]
Date of the Protocol:	13 December 2018
Version of the Protocol:	Final

The confidential information in this document is provided to you as an investigator, potential investigator, or consultant for review by you, your staff and applicable Independent Ethics Committee (IEC) and/or Institutional Review Board (IRB). It is understood that the information will not be disclosed to others without written authorization from Tanvex Biologics Corp. except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

2 SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A double-blinded extension study to provide adjuvant treatment with single agent Herceptin® or TX05 and assess continued safety and immunogenicity in subjects with HER2-positive early breast cancer following neoadjuvant treatment and surgical resection in Protocol TX05-03

PROTOCOL NUMBER: TX05-03E

[redacted] [redacted]

CLINICAL RESEARCH ORGANIZATION SIGNATURE PAGE

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PROTOCOL NUMBER: TX05-03E

[redacted]

Name and Job Title

Date *(day/month/year)*

Signature

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: A double-blinded extension study to provide adjuvant treatment with single agent Herceptin® or TX05 and assess continued safety and immunogenicity in subjects with HER2-positive early breast cancer following neoadjuvant treatment and surgical resection in Protocol TX05-03

PROTOCOL NUMBER: TX05-03E

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 double-blinded extension study to provide adjuvant treatment with single agent Herceptin® or TX05 and assess continued safety and immunogenicity in subjects with HER2-positive early breast cancer following neoadjuvant treatment and surgical resection in Protocol TX05-03

Protocol No.:	TX05-03E
Date of the Protocol:	13 December 2018
Date and 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

<table>
<tr><td>Name of Sponsor/Company:
Tanvex Biologics Corp.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier:

Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Product:
TX05</td></tr>
<tr><td>Name of Active Ingredient:
Trastuzumab</td></tr>
<tr><td colspan="3">Title of Study:
A double-blinded extension study to provide adjuvant treatment with single agent Herceptin® or TX05 and assess continued safety and immunogenicity in subjects with HER2-positive early breast cancer following neoadjuvant treatment and surgical resection in Protocol TX05-03</td></tr>
<tr><td colspan="3">Study Center(s):
This study will only recruit subjects from clinical sites that participated in Study TX05-03.</td></tr>
<tr><td colspan="3">Publication(s):
None.</td></tr>
<tr><td colspan="2">Planned Study Period:
October 2018 to June 2020</td><td>Development Phase:
Phase III</td></tr>
<tr><td colspan="3">Objectives:
• To collect safety, tolerability, and immunogenicity data for single agent Herceptin or TX05 in the adjuvant setting in subjects with early human epidermal growth factor receptor (HER2)-positive breast cancer who completed neoadjuvant treatment and primary resection in Protocol TX05-03.
• To collect safety, tolerability, and immunogenicity data following a single transition from neoadjuvant Herceptin to adjuvant TX05 in this population.
• To collect disease-free survival (DFS) and overall survival (OS) data in this population.</td></tr>
<tr><td colspan="3">Methodology:
This is an extension study for subjects who were treated in the prior TX05/Herceptin neoadjuvant study (Protocol TX05-03) and successfully underwent surgical resection. Eligible subjects will receive adjuvant treatment with single agent Herceptin or TX05 for up to 13 treatment cycles. The study will consist of a Screening period (Days -14 to 0) at least 4 weeks post-surgery to confirm eligibility to continue Herceptin or TX05 treatment, and an adjuvant treatment period (Week 0 [Day 1] to Week 36). All subjects completing the study will attend the End of Study (EOS) Visit at Week 45 (± 7 days). Those discontinuing the study at any time will attend an Early Termination (ET) Visit 9 weeks (± 7 days) after the last administration of study drug.
Subjects fulfilling the eligibility criteria for this extension study will receive intravenous (IV) Herceptin or TX05 (8 mg/kg loading dose then 6 mg/kg) every 3 weeks for 13 cycles, as follows: (1) subjects originally assigned to TX05 in the neoadjuvant study will receive TX05; and (2) subjects originally assigned to Herceptin in the neoadjuvant study will be randomized (1:1) to receive either Herceptin or TX05.
Subjects will attend study visits every 3 weeks until Week 36 (± 3 days). Study procedures include physical examination, vital signs, weight, Eastern Cooperative Oncology Group performance status, clinical laboratory tests, recording of adverse events (AEs), and concomitant medication.
Clinical assessments will be performed before administration of study drug. Clinical laboratory tests will be performed at Screening, Week 0, and then at every other study visit until the EOS/ET Visit. Tumor assessments will be performed at Screening and EOS/ET Visit by means of a computed tomography (CT) scan or magnetic resonance imaging (only if CT scan cannot be performed) of the chest, abdomen, and pelvis.
Cardiac safety will be assessed at Screening and Cycle 6 (Week 15) prior to administration of study drug and at the EOS/ET Visit using 12-lead electrocardiogram (ECG) and echocardiography or multi-gated acquisition 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 before the administration of Cycle 1 (Week 0) and Cycle 6 (Week 15), and at the EOS/ET Visit.</td></tr>
</table>

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	Page:	

Once subjects complete adjuvant treatment with single agent Herceptin or TX05 they may move on to other therapies as recommended by their treating physician. Subjects who prematurely discontinue adjuvant treatment with single agent Herceptin or TX05 may move on to other therapies as recommended by their treating physician, even if they consent to remain in the study.

Number of Subjects:

It is estimated that a minimum of 330 subjects will be enrolled into the double-blind extension study. This estimate is based on 740 subjects completing the neoadjuvant study and approximately 45% of these being eligible to continue treatment in this extension study.

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. Completed neoadjuvant treatment (regardless of treatment arm) in the TX05/ Herceptin neoadjuvant study and the investigator believes the subject requires continued access to single agent trastuzumab in order to continue deriving clinical benefit.
4. Successfully undergone surgical resection of their primary tumor with no evidence of residual disease (as determined by local assessment) and no other adjuvant therapy, other than trastuzumab, is planned. However, subjects will be allowed to receive hormonal therapy if they have hormone receptor positive tumors. Subjects will also be allowed to receive adjuvant radiation therapy, if required by their treating physician.
5. Able to comply with the study protocol.
6. Female subjects of childbearing potential must have a negative serum pregnancy test within 14 days 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 7 months after last administration of study drug.

Exclusion Criteria

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

1. Breast cancer metastases or residual disease post operatively (as determined by local assessment).
2. 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.
3. Lactating or pregnant female.
4. 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 7 months after the last administration of study drug. Subjects must agree to not breast-feed while receiving study drug.
5. Any condition that in the opinion of the Investigator represents an obstacle for study conduct and/or represents a potential unacceptable risk for subjects.

Test Product, Dose, and Mode of Administration:

IV TX05 8 mg/kg loading dose then 6 mg/kg every 3 weeks for 13 cycles.

Reference Therapy, Dose, and Duration of Administration:

IV Herceptin 8 mg/kg loading dose then 6 mg/kg every 3 weeks for 13 cycles.

<table>
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<tr><td>Name of Product:
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Trastuzumab</td></tr>
<tr><td colspan="3">Duration of Treatment:
The study will consist of a Screening period (Days -14 to 0) and a double-blinded adjuvant treatment period (Week 0 [Day 1] to Week 36) and an EOS/ET Visit 9 weeks (± 7 days) after the last administration of study drug.</td></tr>
<tr><td colspan="3">Criteria for Evaluation:
Safety Assessments:
• Treatment-emergent AEs and serious AEs.
• Death.
• Clinical laboratory parameters.
• Vital signs.
• 12-Lead ECG.
• LVEF.
• Physical examination.
Immunogenicity Endpoints:
• Incidence of ADA.
• Incidence of Nab.
Efficacy Endpoints:
• DFS, defined as the time from randomization in the neoadjuvant study (Protocol TX05-03) to the documentation of a first failure, where a failure is the recurrence of breast cancer or a diagnosis of a second primary cancer.
• OS, defined as the time from randomization in the neoadjuvant study (Protocol TX05-03) until death from any cause.</td></tr>
<tr><td colspan="3">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 safety population will include all subjects who are randomized into this extension study and have received at least one dose of study drug. The safety population will be used for all analyses.
The time to event endpoints (DFS and OS) will be summarized using Kaplan-Meier survival curves. The Kaplan-Meier survival estimates, together with the number of subjects, percentage of subjects to experience the event, and the number and percentage of subjects censored will be summarized in a table by treatment group.
No interim analysis is planned.</td></tr>
</table>

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5.1 List of Tables

5.2 List of Figures

5.3 List of Appendices and Supplements

6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
$AUC_{0-\infty}$	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
CI	Confidence interval
C_{max}	Maximum concentration
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
EBC	Early breast cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End of Study
ET	Early Termination
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HER	Human epidermal growth factor receptor
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
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
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition
Nab	Neutralizing antibodies
OS	Overall survival

PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic
T_{max}	Time to maximum concentration
TNFα	Tumor necrosis factor alpha
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 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 levels 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 sample 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, 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 labeled 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% of the dose per gram 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, 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.

This is an extension study for subjects treated in the prior TX05/Herceptin neoadjuvant study (Protocol TX05-03). Subjects who completed the TX05-03 study may be eligible to enroll in this separate protocol designed to further assess and characterize the safety, immunogenicity, 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

- To collect safety, tolerability, and immunogenicity data for single agent Herceptin or TX05 in the adjuvant setting in subjects with early HER2-positive breast cancer who completed neoadjuvant treatment and primary resection in Protocol TX05-03.
- To collect safety, tolerability, and immunogenicity data following a single transition from neoadjuvant Herceptin to adjuvant TX05 in this population.
- To collect disease-free survival (DFS) and overall survival (OS) data in this population.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is an extension study for subjects treated in the prior TX05/Herceptin neoadjuvant study (Protocol TX05-03) and successfully underwent surgical resection. Eligible subjects will receive adjuvant treatment with single agent Herceptin or TX05 for up to 13 treatment cycles. The study will consist of a Screening period (Days -14 to 0) at least 4 weeks post-surgery to confirm eligibility to continue Herceptin or TX05 treatment, and an adjuvant treatment period (Week 0 [Day 1] to Week 36). All subjects completing the study will attend the End of Study (EOS) Visit at Week 45 (± 7 days). Those discontinuing the study at any time will attend an Early Termination (ET) Visit 9 weeks (± 7 days) after the last administration of study drug.

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Subjects will attend study visits every 3 weeks until Week 36 (± 3 days). Study procedures include physical examination, vital signs, weight, Eastern Cooperative Oncology Group (ECOG) performance status, clinical laboratory tests, recording of AEs, and concomitant medication.

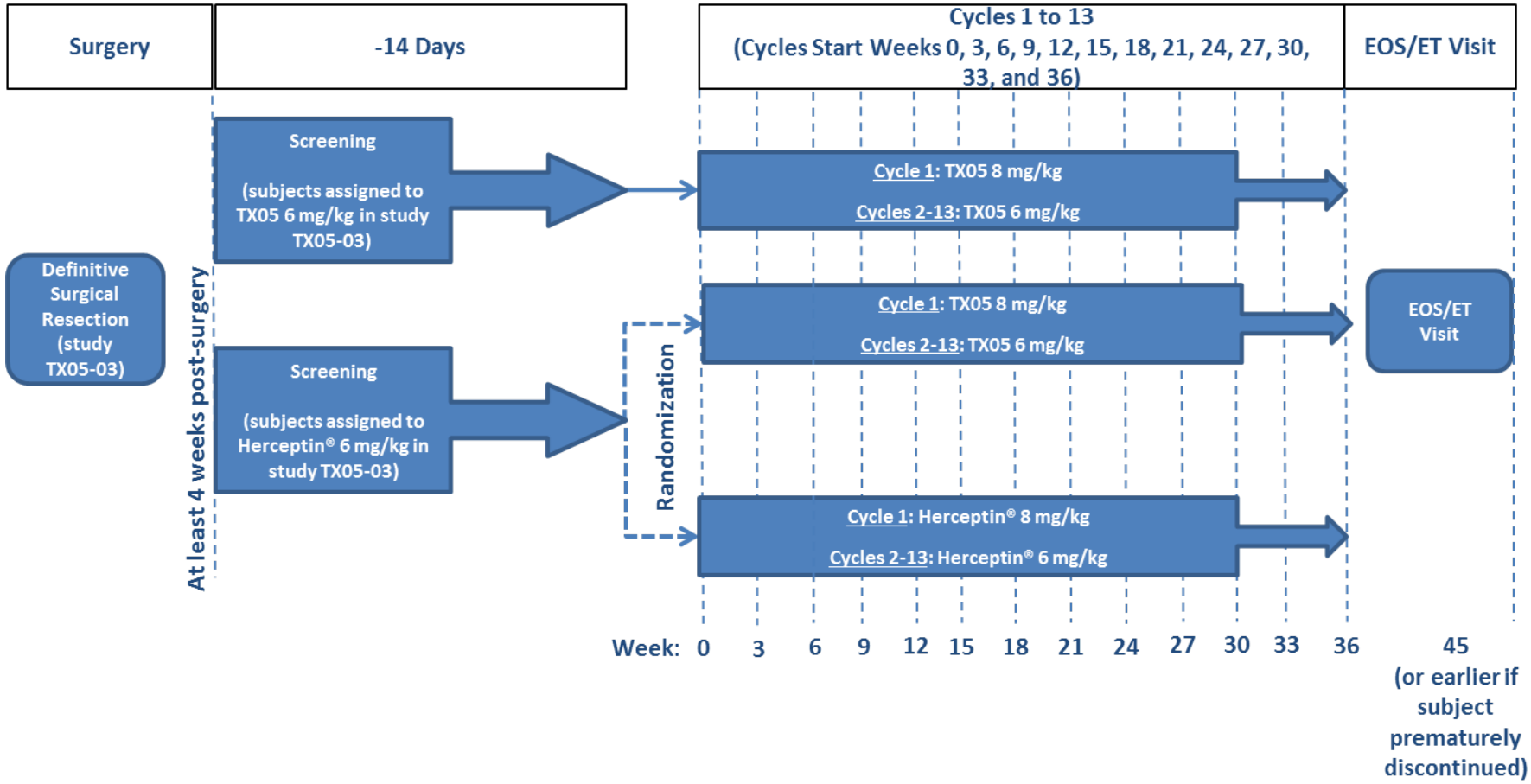
Clinical assessments will be performed before administration of study drug. Clinical laboratory tests will be performed at Screening, Week 0, and then at every other study visit until the EOS/ET Visit. Tumor assessments will be performed at Screening and EOS/ET Visit by means of a computed tomography (CT) scan or magnetic resonance imaging ([MRI] only if CT scan cannot be performed) of the chest, abdomen, and pelvis.

Cardiac safety will be assessed at Screening and Cycle 6 (Week 15) prior to administration of study drug and at the EOS/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 before the administration of Cycle 1 (Week 0) and Cycle 6 (Week 15), and at the EOS/ET Visit.

Once subjects complete adjuvant treatment with single agent Herceptin or TX05 they may move on to other therapies as recommended by their treating physician. Subjects who prematurely discontinue adjuvant treatment with single agent Herceptin or TX05 may move on to other therapies as recommended by their treating physician, even if they consent to remain in the study.

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 (- 14 days)	Adjuvant Cycle (week) TX05 1 (0)	2 (3)	3 (6)	4 (9)	5 (12)	6 (15)	7 (18)	8 (21)	9 (24)	10 (27)	11 (30)	12 (33)	13 (36)	EOS/ET[1] Week 45
Visit Window (days)		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7
Eligibility criteria	X														
Informed consent[2]	X														
Medical & surgical history	X														
Physical examination[3]	X														X
Weight[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests[7]	X	X		X		X		X		X		X		X	X
12-Lead ECG	X						X								X
LVEF (echocardiography or MUGA)[8]	X						X								X
Randomization		X													
Study drug administration[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity sampling[10]		X					X								X
Tumor assessment[11]	X														X
AE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Screening (- 14 days)	Adjuvant Cycle (week) TX05 1 (0)	2 (3)	3 (6)	4 (9)	5 (12)	6 (15)	7 (18)	8 (21)	9 (24)	10 (27)	11 (30)	12 (33)	13 (36)	EOS/ET[1] Week 45
Subject compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X

ADA: anti-drug antibodies; AE: adverse event; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS/ET: End of Study/Early Termination; IV: intravenous; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; MUGA: multi-gated acquisition; Nab: neutralizing antibodies.

1. All subjects completing adjuvant treatment will attend the EOS/ET Visit 9 weeks (± 7 days) after the last administration of study drug. Subjects that withdraw from treatment due to disease progression, but consent to stay in the study, will attend the ET visit 9 weeks (± 7 days) after the last administration of study drug and thereafter continue to be followed up by telephone for overall survival status every 6 weeks until Week 45 (± 7 days). Subjects that withdraw from treatment for any other reason than disease progression, and consent to remain in study, will continue to attend the scheduled study visits including the EOS visit. In the event that such a subject subsequently experiences disease progression, he/she will attend the ET visit 9 weeks (± 7 days) after the last administration of study drug if this has not already occurred, and thereafter be followed-up by telephone for overall survival status every 6 weeks until Week 45 (± 7 days). Subjects completely discontinuing from study will attend the ET visit 9 weeks (± 7 days) after the last administration of study drug and no further data will be collected.
2. Informed consent must be obtained prior to undergoing any study-specific procedure and may occur prior to the 14-day Screening period.
3. Complete physical examinations will be conducted at Screening and at the EOS/ET Visit. All other evaluations will be at the discretion of the investigator. Height will be recorded at Screening only.
4. Weight will be recorded at Screening and Day 1 of each cycle and as clinically indicated. The weight from Day 1 of each cycle should be used to calculate the dosage of study drug to be administered.
5. Temperature, blood pressure, pulse rate, and respiratory rate will be recorded at each timepoint.
6. Subjects of childbearing potential will have a blood serum pregnancy test at Screening and at the EOS/ET Visit. A urine pregnancy test will also be performed prior to each treatment cycle to exclude potential pregnancy.
7. Clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be performed by local laboratories. Clinical laboratory tests can be performed at other visits at the discretion of the investigator.
8. LVEF (echocardiography or MUGA) should be assessed as clinically indicated during the adjuvant treatment period.
9. Subjects will receive up to 13 cycles of adjuvant chemotherapy: Herceptin or TX05 8 mg/kg body weight will be administered by 60-minute IV infusion, on Day 1 of treatment Cycle 1 and thereafter 6 mg/kg body weight every 3 weeks until Cycle 13.

10. Serum samples for detection of ADA and Nab will be collected before the administration of study drug at Cycle 1 (Week 0) and Cycle 6 (Week 15), and at the EOS/ET Visit.
11. CT scan or MRI, only if CT scan cannot be performed, of chest, abdomen, and pelvis.

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)**	**Cycle 9 (Week 24)**	**Cycle 10 (Week 27)**	**Cycle 11 (Week 24)**	**Cycle 12 (Week 24)**	**Cycle 13 (Week 24)**	**EOS/ET Visit**
Hematology	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
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 standard of care (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 -14 days

Subjects are to undergo a Screening Visit 14 days prior to the planned first day of study treatment. Screening assessments are as follows:

- Assess eligibility criteria
- Obtain written informed consent
- Record medical and surgical history
- Perform physical examination (including height at Screening only)
- Record weight
- Record vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Perform pregnancy test (for subjects of childbearing potential) (within 14 days of first administration of study drug)
- Assess ECOG performance status (Appendix 1)
- Perform clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Perform 12-lead ECG
- Assess LVEF (echocardiography or MUGA)
- Perform tumor assessment

9.1.2.2 Treatment Period: TX05/Herceptin: Cycle 1 (Week 0) to Cycle 13 (Week 36)

Cycle 1 (Week 0)

- Randomization (subjects originally assigned to Herceptin in the TX05-03 study will be randomized [1:1] to receive either Herceptin or TX05; subjects originally assigned to TX05 in the TX05-03 study will continue to receive TX05)
- Record weight
- Record vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Perform pregnancy test (for subjects of childbearing potential)
- Assess ECOG performance status (Appendix 1)
- Perform clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Study drug administration
- Perform immunogenicity sampling
- Record AEs
- Assess subject compliance
- Record concomitant medications

Cycle 2 (Week 3) to Cycle 13 (Week 36)

- Record weight
- Record vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Perform pregnancy test (for subjects of childbearing potential)
- Assess ECOG performance status (Appendix 1)
- Perform clinical laboratory tests ([hematology, clinical chemistry, urinalysis] Cycle 3, Cycle 5, Cycle 7, Cycle 9, Cycle 11, and Cycle 13 only)
- Perform 12-lead ECG (Cycle 6 only)
- Assess LVEF ([Cycle 6 only] echocardiography or MUGA)
- Study drug administration
- Perform immunogenicity sampling (Cycle 6 only)
- Record AEs
- Assess subject compliance
- Record concomitant medications

9.1.2.3 End of Study Visit (Week 45)/Early Termination Visit

- Perform physical examination
- Record vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Perform pregnancy test (for subjects of childbearing potential)
- Perform clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Perform 12-lead ECG
- Assess LVEF (echocardiography or MUGA)
- Perform immunogenicity sampling
- Perform tumor assessment
- Record AEs
- Record concomitant medications

9.2 Discussion of Study Design

This study will evaluate the similarity in long-term safety, efficacy, and immunogenicity of TX05 compared to Herceptin in subjects for whom adjuvant 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.

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[15,16,17]. 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.

The efficacy endpoints assessed in this study (DFS and OS) are commonly used endpoints in oncology trials with OS traditionally regarded as the ultimate measure of treatment benefit.

Trastuzumab given every 3 weeks (8 mg/kg loading dose then 6 mg/kg dose) is per the US Herceptin label for EBC[18]. For this intended biosimilar, TX05, subjects with HER2-positive EBC following neoadjuvant treatment and surgical resection provides a sensitive and uniform population of subjects.

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). Prior to the TX05-03 study, 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 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. Completed neoadjuvant treatment (regardless of treatment arm) in the TX05/ Herceptin neoadjuvant study and the investigator believes the subject requires continued access to single agent trastuzumab in order to continue deriving clinical benefit.

4. Successfully undergone surgical resection of their primary tumor with no evidence of residual disease (as determined by local assessment) and no other adjuvant therapy, other than trastuzumab, is planned. However, subjects will be allowed to receive hormonal therapy if they have hormone receptor positive tumors. Subjects will also be allowed to receive adjuvant radiation therapy, if required by their treating physician.
5. Able to comply with the study protocol.
6. Female subjects of childbearing potential must have a negative serum pregnancy test within 14 days 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 7 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. Breast cancer metastases or residual disease post operatively (as determined by local assessment).
2. 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.
3. Lactating or pregnant female.
4. 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 7 months after the last administration of study drug. Subjects must agree to not breast-feed while receiving study drug.
5. Any condition that in the opinion of the Investigator represents an obstacle for study conduct and/or represents a potential unacceptable risk for subjects.

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) EOS procedures should be performed.

If it is necessary to discontinue the study drug earlier than planned then:

- Subjects that withdraw from treatment due to disease progression, but consent to stay in the study, will attend the ET visit 9 weeks (± 7 days) after the last administration of study drug

and thereafter continue to be followed up by telephone for overall survival status every 6 weeks until Week 45 (± 7 days). Subjects that withdraw from treatment for any other reason than disease progression, and consent to remain in study, will continue to attend the scheduled study visits including the EOS visit. In the event that such a subject subsequently experiences disease progression, he/she will attend the ET visit 9 weeks (± 7 days) after the last administration of study drug if this has not already occurred, and thereafter be followed-up by telephone for overall survival status every 6 weeks until Week 45 (± 7 days).

- Subjects completely discontinuing from study will attend the ET visit 9 weeks (± 7 days) after the last administration of study drug and no further data will be collected.

Subjects who discontinue treatment 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.

Subjects that withdraw from treatment, but consent to stay in the study, may move on to other therapies as recommended by their treating physician.

Subjects who withdraw from treatment for any reason or completely withdraw from the study for any reason prior to the EOS Visit should complete the procedures scheduled for that visit (ET Visit) 9 weeks (± 7 days) after the last administration of study drug.

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 dose (6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent doses should be administered 21 days later according to the 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 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 150 mg or 420 mg of TX05, sufficient to deliver 150 mg or 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 immunoglobulin-based drug products.

Subjects will receive up to 13 cycles of adjuvant chemotherapy. TX05 or Herceptin 8 mg/kg body weight will be administered by 60-minute IV infusion on Day 1 of treatment Cycle 1 and thereafter 6 mg/kg body weight every 3 weeks until Cycle 13.

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

10.2 Treatment Regimen Adjustments

Dose modification guidelines are provided in Appendix 2.

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. 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. In order to maintain the study blind, all eligible subjects will be randomized within the IWRS for this extension study. Subjects originally assigned to TX05 in the neoadjuvant study protocol TX05-03 will continue to receive TX05 in this extension study. Subjects originally assigned to Herceptin in the neoadjuvant study will be randomized (1:1) before the administration of study drug at Cycle 1 (Week 0) to receive either Herceptin or TX05. 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.

10.7 Concomitant Therapy

Concomitant medications administered for any reason must be locally-approved and with 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.

Subjects will be allowed to receive hormonal therapy during adjuvant treatment with single agent Herceptin or TX05 if they have hormone receptor positive tumors.

It is not anticipated that subjects who have undergone surgical resection of their primary tumor with no evidence of residual disease would require radiation therapy, but if required by their treating physician, subjects can receive adjuvant radiation therapy during TX05 or Herceptin therapy.

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 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 EOS/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 Safety Endpoints:

- TEAEs and SAEs.
- Death.
- Clinical laboratory parameters.
- Vital signs.
- 12-lead ECG.
- LVEF.
- Physical examination.

11.1.2 Immunogenicity Endpoints:

- Incidence of ADA.
- Incidence of Nab.

11.1.3 Efficacy Endpoints

- DFS, defined as the time from randomization in the neoadjuvant study (Protocol TX05-03) to the documentation of a first failure, where a failure is the recurrence of breast cancer or a diagnosis of a second primary cancer.
- OS, defined as the time from randomization in the neoadjuvant study (Protocol TX05-03) until death from any cause.

11.2 Tumor Assessment

A CT scan or MRI (only if CT scan cannot be performed) of the chest, abdomen, and pelvis is required at Screening for all subjects.

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 all other aspects of the chest.

Final tumor assessment at the EOS/ET Visit will include repeat CT scan or MRI (only if CT scan cannot be performed) of the chest, abdomen, and pelvis. Assessments are not to be scheduled based on the scheduled calendar date of the EOS/ET Visit.

11.3 Echocardiogram/MUGA

Assessment of LVEF using an echocardiogram or MUGA scan will be performed at Screening, prior to dosing at Cycle 6 (Week 15), at the EOS/ET Visit, and as clinically indicated during the adjuvant treatment period. The modality used for individual subjects should be consistent throughout the study.

11.4 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
Complete blood count with differential	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.

All tests will be performed by local laboratories.

11.5 Electrocardiogram Assessments

12-lead ECGs will be performed at Screening, prior to dosing at Cycle 6 (Week 15), and at the EOS/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.

11.6 Physical Examination

Complete physical examinations will be conducted at Screening and at the EOS/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 will be recorded at Screening and Day 1 of each cycle, and as clinically indicated. The weight from Day 1 of Cycles 1 to 13 should be used to calculate the dosage of trastuzumab to be administered.

11.7 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.

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 1 (Week 0), Cycle 6 (Week 15), and at the EOS/ET Visit.

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. A serum separator tube 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.

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 principal 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 EOS Visit should be considered an AE.

Ongoing drug-related AEs and SAEs from the neoadjuvant study (Protocol TX05-03) and any SAEs that occurred after completion of the neoadjuvant study will be recorded at Screening in the subject’s medical history, while AEs occurring in this extension study will be recorded from Day 1 (Week 0) of Cycle 1 of study treatment.

All ongoing AEs in this extension study should be followed up until the EOS/ET Visit, with the exception of any ongoing study drug-related AEs, which should be followed until the event is resolved, considered stable, or the investigator determines the AE is no longer clinically significant.

At any time after the EOS/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, 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 (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 and at the EOS/ET Visit 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 24 hours (i.e. immediately but no later than 24 hours) of when he or she becomes aware of it.

All SAE reports must be emailed to the following address within 24 hours (fax may be used if sending by email fails or is not possible for any reason):

[redacted] DRUG SAFETY (Pharmacovigilance Department)

Europe and Asia Pacific

[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 endpoint definitions and/or analyses will also be reflected in a protocol amendment.

13.1 Sample Size and Power

It is estimated that a minimum of 330 subjects will be enrolled into this double-blinded extension study. This estimate is based on 740 subjects completing the neoadjuvant study (TX05-03) and approximately 45% of these being eligible to continue treatment in this extension study.

13.2 Analysis Populations

13.2.1 Safety Population

The safety population will include all subjects who are enrolled into this extension study and have received at least one dose of study drug (TX05 or Herceptin) in the adjuvant treatment phase. The safety population will be used for all analyses.

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 (TX05 only, Herceptin only, and Herceptin/TX05 transition) for all analyses. If there are any cases where subjects received both drugs in the adjuvant setting (TX05-03), they will be assigned to the treatment initially given in this extension study.

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 completing the study/withdrawing early (including withdrawal reason)
- Subject allocation by site

13.3.5 Safety Analysis

The safety parameters will include the following:

- TEAE and SAE
- Death
- Clinical laboratory parameters
- Vital signs
- 12-Lead ECG
- LVEF
- 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. Drug-related TEAEs and SAEs will be also summarized by treatment group (TX05 only, Herceptin only, and Herceptin/TX05 transition).

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.

13.3.6 Immunogenicity Assessment

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

13.3.7 Efficacy Analysis

Efficacy will be assessed using the time to event endpoints DFS and OS. DFS is defined as the time from randomization in the neoadjuvant study (Protocol TX05-03) to the documentation of a first failure, where a failure is the recurrence of breast cancer or a diagnosis of a second primary cancer.

OS is defined as the time from randomization in the neoadjuvant study (Protocol TX05-03) until death from any cause.

DFS and OS will be summarized using Kaplan-Meier survival curves. The Kaplan-Meier survival estimates, together with the number of subjects, percentage of subjects to experience the event, and the number and percentage of subjects censored will be summarized in a table by treatment group.

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 standard operating procedures 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 principal 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 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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 2 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