STATISTICAL ANALYSIS PLAN

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

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Final Analysis
Statistical Analysis Plan (SAP)

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

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On behalf of:

Tanvex Biologics Corp.

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REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
Final 1.0/ 19-Dec-2019	Baseline version	N/A	N/A
Version 2.0/ 20-Jul-2020	Final Version 2.0	7.2.2.1 Partial Dates for Adverse Events	Updated imputation rule of AE start date.
Version 2.0/ 20-Jul-2020	Final Version 2.0	7.2.2.2 Missing Causality and Severity for Adverse Events	Added details of Causality imputation rule for clarify.
Version 2.0/ 20-Jul-2020	Final Version 2.0	8.2 General statistical conventions	Added additional condition for baseline.
Version 2.0/ 20-Jul-2020	Final Version 2.0	8.4.2 Baseline characteristics	Added additional information for baseline summary.
Version 2.0/ 20-Jul-2020	Final Version 2.0	8.7.1 Adverse events	Updated definition for TEAEs.
Version 2.0/ 24-Jul-2020	Final Version 2.0	8.6.2.1 Disease-Free Survival (DFS)	Updated on Censoring rule for DFS.
Version 2.0/ 04-MAR-2022	Final Version 2.0	8.4.4 Concomitant medications	Update ATC 2 to ATC 1
Version 2.0/ 07-MAR-2022	Final Version 2.0	7.1 Derived Variables 8.1 General statistical conventions	Added additional information for baseline summary.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
AEs	Adverse events
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CI	Confidence interval
CS	Clinically Significant
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
ECOG	Eastern cooperative oncology group
EOS	End of study
ET	Early termination
HER2	Human epidermal growth factor receptor
ICH	International conference on harmonization
IWRS	Interactive web response system
LVEF	Left ventricular ejection fraction
MedDRA	Medical dictionary for regulatory affairs
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition
Nab	Neutralizing antibodies
NCS	Not Clinically Significant
OS	Overall survival
PT	Preferred terms
SAE	Serious adverse events
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAEs	Treatment-emergent AEs
WHODDE	World health organization drug dictionary enhanced

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol TX05-03E, final version "A double-blinded extension study to provide adjuvant treatment with single agent Herceptin® or TX05 and assess continued safety and immunogenicity in subjects with human epidermal growth factor receptor (HER2) - positive early breast cancer following neoadjuvant treatment and surgical resection in Protocol TX05-03" dated 13December2018 for final analysis. The table of contents and templates for the TFLs will be produced in a separate document.

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

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

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

2 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.

3 STUDY DESIGN

3.1 General study design

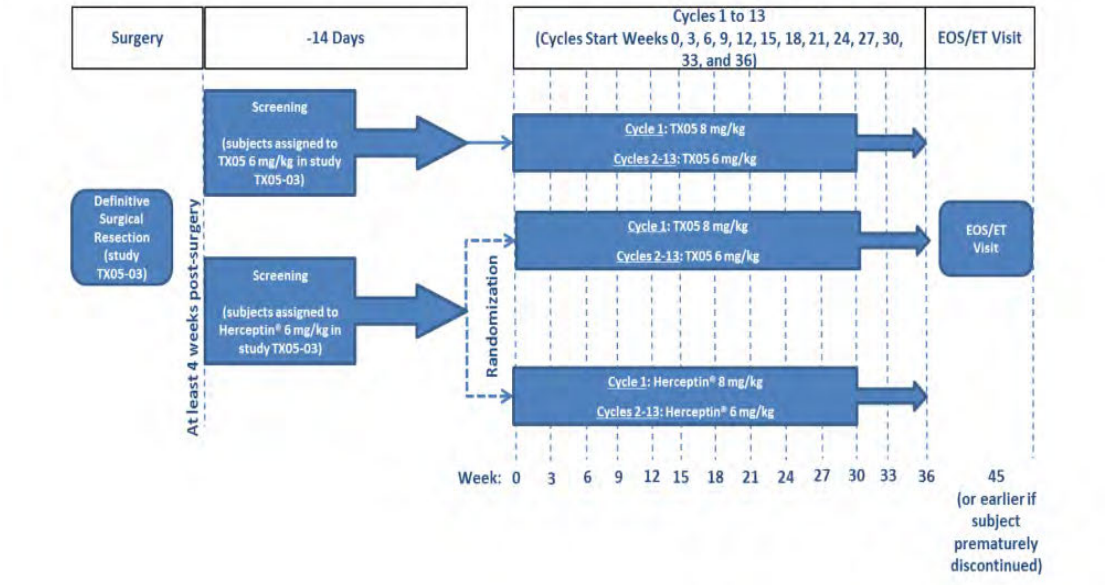
This is an extension study for subjects who have completed the TX05/Herceptin neoadjuvant study (Protocol TX05-03) and successfully underwent surgical resection. Eligible subjects will receive adjuvant treatment with single agent Herceptin or TX05 for up to 13 treatment cycles. The study will consist 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 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.

This study will only recruit subjects from clinical sites that participated in study TX05-03 and approximately 330 subjects are anticipated to be enrolled into the double-blinded extension study.

The Study Flow Chart is presented in Figure 1.

Figure 1: Study Flow Chart



3.2 Randomization and blinding

Both randomization and blinding techniques will be used in this study to minimize bias. This is a double-blinded study and randomized treatment assignments will be blinded to the subject, investigator/study staff and sponsor's study team conducting the study. 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.

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.

3.3 Study treatments and assessments

Eligible subjects from protocol TX05-03 will receive Herceptin or TX05 treatment during an adjuvant treatment period of up to 13 cycles (Week 0 [Day 1] to Week 36).

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 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.

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.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Scheduled of Study Assessments in Table 1 below.

Table 1: Schedule of Study Assessments

Study Procedure	Screening (-14 days)	Adjuvant Cycle (week) TX05													EOS/ ET[1] Week 45
		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)	
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
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 2.

Table 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 30)	Cycle 12 (Week 33)	Cycle 13 (Week 36)	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.

4 STUDY ENDPOINTS

4.1 Efficacy endpoints

- Disease-free survival (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.
- Overall Survival (OS), defined as the time from randomization in the neoadjuvant study (Protocol TX05-03) until death from any cause.

4.2 Safety endpoints

The safety endpoints of this study are:

- Treatment-emergent AEs (TEAEs) and Serious Adverse Events (SAEs).
- Death.
- Clinical laboratory parameters.
- Vital signs.
- 12-lead ECG.
- Left ventricular ejection fraction (LVEF).
- Physical examination.

4.3 Immunogenicity endpoints

- Incidence of ADA.
- Incidence of Nab.

5 SAMPLE SIZE AND POWER

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

6 ANALYSIS POPULATIONS

6.1 Safety population (Safety)

The safety population will include all subjects who are enrolled into TX05-03E 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.

7 STATISTICAL CONSIDERATIONS AND ANALYSIS

7.1 Derived Variables

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

Variables	Formula
Demographic and Baseline characteristics	
Age at informed consent (in years)	Year of informed consent – year of birth + 1
Date of Administration of Study Drug	
First date of study drug administration	The minimum date of non-zero dose of study treatment (TX05 or Herceptin)
Last date of study drug administration	The maximum date of non-zero dose of study treatment (TX05 or Herceptin)
Baseline Derivations	
Baseline	Last observation prior to the date and time or date of the first dose of study drug.
Change from baseline	Post baseline value – Baseline
Study day	
Study day	Event or Assessment date – First dose date of study treatment in cycle 1 +1 The study day will be displayed in data listings.

7.2 Handling of missing data and outliers

7.2.1 Missing data analysis methods

Missing values will not be imputed, unless otherwise specified.

7.2.2 Handling of missing or incomplete dates

7.2.2.1 Partial Dates for Adverse Events

When only day is missing:

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

For start date of an AE:

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

  Otherwise,

- If the AE stop date is prior to first dose date of Cycle 1, impute the AE start day as 1
- If the AE stop date is on or after first dose date of Cycle 1 medication:
  - If month and year of onset date are the same as month and year of the first dose date in Cycle 1, impute AE start day as day of first dose date in Cycle 1
  - Else if the month and year of onset date are after the month and year of the first dose date in the Cycle 1, impute AE start day as 1

When only day and month are missing:

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

For start date of an AE:

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

Otherwise,

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

If Year of AE start date is missing:

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

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

7.2.2.2 Missing Causality and Severity for Adverse Events

When the causality of the AE is missing:

- If the causality of AEs is missing, causality will not be imputed for AEs prior to the first dose of Cycle 1
- Causality will be imputed as "Possibly related" for AEs which occurred started on or after the first dose of Cycle 1.

When the severity of AEs is missing:

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

7.2.2.3 Missing or partial dates for concomitant medication

When only day is missing:

- If it is the start date of the medication prior to the first dose of Cycle 1, the first day of the month will be used.
- If it is the start date of the medication after first dose of Cycle 1:
  - If month and year is equal to the month and year of the first dose of Cycle 1, then the day of the first dose in Cycle 1 will be used;
  - Else the first day of the month will be used.
- If it is the end date of the medication, then the last day of the month will be used.

When day and month are missing:

- If it is the start date of the medication prior to the first dose of Cycle 1, January 1st of the year will be used.
- If it is the start date of the medication after first dose of Cycle 1:
  - If year is equal to the year of first dose in Cycle 1, then the day and month of the first dose in Cycle 1 will be used;
  - Else January 1st of the year will be used,
- If it is the end date of the medication, then December 31st of the year will be used.

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

8 STATISTICAL METHODS

8.1 General statistical conventions

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

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

In general, continuous variables will be summarized using the following standard descriptive summary statistics: number of observations, arithmetic mean, standard deviation (SD), minimum, median, and maximum. Categorical variables will be displayed by means of frequency tables including percentages. Safety population will be used for all analysis, unless otherwise specified.

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 neoadjuvant study (Protocol TX05-03), they will be assigned to the treatment initially given in this extension study. Unless otherwise specified the lay out of the treatment group in the output will be as below:

TX05 only	Herceptin Only	Herceptin/TX05 transition	Overall

TX05 only: Subject took TX05 in neoadjuvant study (Protocol TX05-03) and continued same treatment in study TX05-03E

Herceptin Only: Subject took Herceptin in neoadjuvant study (Protocol TX05-03) and randomized to Herceptin in study TX05-03E

Herceptin/TX05 transition: Subject took Herceptin in neoadjuvant study (Protocol TX05-03) and randomized to TX05 in study TX05-03E

Baseline is defined as the last non-missing assessment with a collection date and time or date prior to the first dose of cycle 1 study treatment in extension study (TX05-03E).

8.2 Subject disposition

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

- Number of subjects screened
- Number of subjects randomized
- Number of subjects treated (Safety population)
- Number and percent of subjects receiving study drug (TX05 or Herceptin)
- Number and percent of subjects received all doses of drug as per protocol/ withdrawing early (including withdrawal reason)
- Number and percent of subjects completing the study/withdrawing early

(including withdrawal reason)

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

Subject allocation by site will be summarized.

8.3 Protocol deviations

Protocol deviations for given categories or subcategories will be summarized by count and percentages. Percentages will be based on safety population. Additionally, listings will also be provided for protocol deviations.

8.4 Demographics and baseline characteristics

8.4.1 Demographics

Demographic and baseline characteristics will be analyzed descriptively and results will be presented overall and by treatment group. The data collected in neoadjuvant study (Protocol TX05-03) will be used for the demographic summary except age, height and weight.

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

Continuous demographic variables age, height, weight and BMI will be summarized by descriptive statistics. Age will be calculated based on the informed consent date.

Demographics will be listed for all enrolled subjects.

8.4.2 Baseline characteristics

The categorical baseline characteristics such as estrogen receptor (ER) status, progesterone receptor (PR) status, hormone receptor (HR) status, tumor stage, ECOG performance status, Baseline Overall Interpretation of ECG, Viral disease (HBsAg, HBcAb, HCV, and HIV), will be summarized using frequency counts and percentage by treatment group. Continuous variable LVEF will be summarized by descriptive statistics. The data collected in neoadjuvant study (Protocol TX05-03) will be used for the baseline summary except for ECOG performance status, overall interpretation of ECG and LVEF.

Baseline characteristics will be listed for all subjects enrolled in the study TX05-03E.

8.4.3 Medical history

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

Any Serious event occurring after the neoadjuvant study's (Protocol TX05-03) surgery and before extension study TX05-03E's informed consent signature, as well as the neoadjuvant study's (Protocol TX05-03) ongoing and drug related AEs or SAEs will be reported as medical history.

Medical history data will be listed by subjects.

8.4.4 Concomitant medications

Medications used in this study will be coded by using the latest available version of the World Health Organization Drug Dictionary Enhanced (WHODDE).

Concomitant medications: are defined as those medications with a start date on or after the first dose of study drug.

Concomitant medications will be summarized descriptively using frequency tables by Anatomical Therapeutic Chemical (ATC) class 1 and preferred name by treatment group and overall on the safety set.

Concomitant medications and concomitant surgeries /procedures will be listed by subjects.

8.5 Extent of exposure

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

Treatment exposure will be presented for TX05 only, Herceptin only and Herceptin/TX05 transition separately using the safety population and will be listed appropriately.

8.5.1 Treatment duration

Descriptive statistics will be provided by study treatment group (By TX05 only, Herceptin only and Herceptin/TX05 transition) for the following:

- Number of cycles
- Duration of exposure (weeks)

Durations (weeks) are defined as the following,

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

8.5.2 Cumulative Dose

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

- Total TX05 dose administered (mg/kg)
- Total Herceptin dose administered (mg/kg)

8.5.3 Treatment compliance

Relative dose intensity is defined as following,

Relative Dose Intensity = ([total dose administered in mg/kg]/ [planned total dose])*100

Where, Planned total dose = prescribed starting dose × number of cycles.

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

8.6 Efficacy analyses

8.6.1 Analysis methods

The analyses of the efficacy endpoints will be performed using the safety population.

8.6.1.1 Multiplicity

Not applicable.

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

Not applicable.

8.6.2 Analysis of efficacy endpoints

Efficacy will be assessed using the time to event endpoints disease-free survival (DFS) and overall survival (OS).

8.6.2.1 Disease-Free Survival (DFS)

DFS is defined as the time from randomization in the neoadjuvant study TX05-03 to the documentation of a first failure, where a failure is the recurrence of breast cancer, a diagnosis of a second primary cancer.

Recurrence or a diagnosis of a second primary cancer will be estimated as below (based on CRF variable)

Target lesion	If organ =Breast	longest diameter >0 or Dimension not measurable= Too small to measure
	If organ= other than breast	Sum of diameter >0
Non Target lesion	Lesion evaluation = Present or Increased	

Censoring rule for DFS:

No recurrence of breast cancer and no diagnosis of a second primary cancer	Date of last evaluable tumor assessment	Censored
Discontinued from study	Date of last evaluable assessment	Censored
No post baseline or no evaluable post baseline assessment	Date of first dose	Censored

No baseline or no evaluable baseline assessment	Date of first dose	Censored
Death	Date of last evaluable assessment	Censored

8.6.2.2 Overall Survival (OS)

OS is defined as the time from randomization in the neoadjuvant study TX05-03 until death from any cause. Subjects will be censored for this endpoint on the date of the last known date alive if they do not die.

DFS and OS will be summarized using Kaplan-Meier (K-M) method. The number and percentage of subjects experience the event, and the number and percentage of subjects censored will be summarized in a table by treatment group.

Rates at fixed time points (month) will be derived from the K-M estimate and corresponding confidence interval will be derived based on Greenwood formula.

In addition, the median and quartiles (25th & 75th) with 95% confidence interval (CI) will be provided using Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). K-M plot of DFS and OS will be provided separately using safety population by treatment group.

K-M plot of DFS and OS for safety population will be provided.

All tumor assessments, DFS and OS data will be listed by subjects.

8.7 Safety analyses

The safety parameters will include the following:

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

These analyses will be performed using the safety population.

8.7.1 Adverse events

Treatment-emergent AEs (TEAEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), and graded according to Common Terminology Criteria for Adverse Events (CTCAE). TEAEs will be analyzed using frequency counts and percentages by system organ class (SOC) and MedDRA preferred term (PT), graded, by

treatment group (TX05 only, Herceptin only, Herceptin/TX05 transition) and overall.

TEAEs: AEs newly occurring on or after the first dose of study drug of study TX05-03E or severity becomes worse on or after the first dose of study drug of the study TX05-03E.

TEAEs will be summarized separately based on the definitions mentioned above by treatment group and overall. AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- Study drug related TEAEs
- TEAEs leading to discontinuation of study treatment
- TEAEs by maximum severity grade
- Serious TEAEs
- Study drug related serious TEAEs
- Serious TEAEs leading to discontinuation of study treatment
- TEAEs leading to death.
- Serious TEAEs leading to death.

The above listed TEAEs will be summarized by SOC, PT for each treatment group and overall using frequency counts and percentages (i.e., number and percentage of subjects with an event). In addition, an overall summary for the categories described above will be summarized by treatment group.

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

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

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

When reporting adverse events by severity, only the most severe occurrence will be included in the incidence.

All AEs will be listed. Additional listings will be provided for AEs leading to discontinuation of study drug and serious AEs.

Listing of death will also be provided separately.

8.7.2 Clinical laboratory evaluations

Clinical safety laboratory data will be presented by treatment group and overall for each scheduled visit. For laboratory tests with quantitative values, descriptive statistics (number of subjects, mean, median, SD, min, and max) of the observed values and changes from baseline at each scheduled visits will be reported by treatment group and overall. For laboratory tests with categorical values, the number and percent of subjects in each category will be summarized by treatment group at each scheduled visit. Shift tables for values outside the normal ranges will be presented as appropriate.

Listings will be produced for all laboratory parameters collected.

8.7.3 Vital signs

Observed values and changes from baseline for vital sign measurements (weight, temperature, blood pressure (systolic/diastolic), pulse rate, and respiratory rate) will be summarized by treatment group and overall for each scheduled visit.

A listing will be produced for all vital signs collected.

8.7.4 Physical examinations

All physical examination data and abnormalities (Normal, Abnormal- Not Clinically Significant (NCS), Abnormal- Clinically Significant (CS) and Not Examined) will be summarized by treatment group and overall for each scheduled visit (baseline (screening) and End of Study (EOS)/ Early Termination (ET) visit). Shift tables from baseline to EOS/ET (normal/abnormal) assessments will be provided by treatment group and overall.

A listing will be produced for all physical examination data.

8.7.5 Electrocardiograms

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

Shift tables from baseline to each post baseline scheduled protocol assessment visit (normal/abnormal (NCS, CS)) assessments will be provided by treatment group and overall.

Clinically notable abnormalities with thresholds of:

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

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

will be summarized by treatment group at each ECG scheduled visits using count and percentage.

A listing will be produced for all ECG measurements collected.

8.7.6 Other safety assessments

8.7.6.1 ECOG

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

A listing will be produced for all ECOG data collected.

8.7.6.2 Pregnancy

Pregnancy test results will be listed.

8.7.6.3 LVEF

Observed values and changes from baseline at each visit for LVEF will be summarized by treatment group and overall for each scheduled protocol assessment visit.

In addition, LVEF quantitative values will be classified into the following 4 categories and will be summarized using count and percentage:

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

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

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

Severe dysfunction = LVEF less than 30%

A listing will be produced for all LVEF.

8.8 Other analysis

8.8.1 Immunogenicity analyses

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

Immunogenicity data (ADA and Nab) will be listed.

8.9 Interim analysis

Not Applicable

9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

Not applicable.

10 REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95 - adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).

11 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 than3 occasions for cardiomyopathy

Symptomatic cardiac failure	• Hold trastuzumab, monitor LVEF and seek cardiology input