Clinical Study Protocol

Protocol Title:	Double-blind, Randomized, Multicenter, Phase III Clinical Study to Compare the Efficacy and to Evaluate the Safety and Immunogenicity of Trastuzumab Biosimilar HLX02 and EU-sourced Herceptin® in Previously Untreated HER2-Overexpressing Metastatic Breast Cancer
Protocol Number:	HLX02-BC01
Date of Protocol:	17 JULY 2017 v5.0 (Final version)
Product:	HLX02 (trastuzumab)
EUDRACT No.:	2016-000206-10
Study Phase:	III
Sponsor:	Shanghai Henlius Biotech, Inc. 1F, Building A, 150 Copernicus Road China (Shanghai) Pilot Free Trade Zone
Project Managers:	**Black Li** Shanghai Henlius Biotech, Inc. as above **Fanny Chong** Quintiles Hong Kong Ltd Unit 2212-19, Level 22, Metroplaza Tower 1 22 Hing Fong Road, Kwai Fong New Territories, Hong Kong
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International Study Coordinator:	**Binghe Xu**, MD, PhD Cancer Hospital, Chinese Academy of Medical Sciences Panjiayuan, Chaoyang District Beijing 100021, P.R. China **Telephone number: +86 1087788826**

Signature of Sponsor

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PROTOCOL NO: HLX02-BC01

Mingqi Lu 17JUL2017

Mingqi Lu **Date**

Senior Vice President
Shanghai Henlius Biotech, Inc.

Signature of International Study Coordinator

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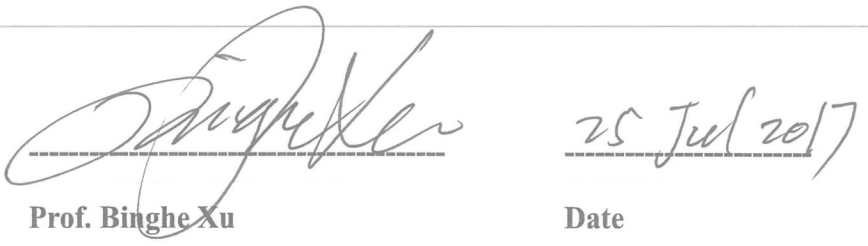
PROTOCOL NO: HLX02-BC01



25 Jul 2017

Prof. Binghe Xu **Date**

International Study Coordinator
Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Synopsis

Name of Sponsor/Company:	Shanghai Henlius Biotech, Inc
Name of Finished Product: **Experimental Drug:**	Not applicable HLX02
Name of Comparator:	Herceptin®
Name of Active Ingredient:	Trastuzumab
Title of Study:	Double-blind, Randomized, Multicenter, Phase III Clinical Study to Compare the Efficacy and to Evaluate the Safety and Immunogenicity of Trastuzumab Biosimilar HLX02 and EU-sourced Herceptin® in Previously Untreated HER2-Overexpressing Metastatic Breast Cancer
Protocol No:	HLX02-BC01
Investigators:	International study coordinator Binghe Xu at the Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China
Study center(s):	Approximately 83 study centers worldwide

Study period: Screening (up to 28 days), Treatment Period (maximum 12 months), Safety Follow-up (30 days after last dose of study drug), Survival Follow-up (up to 36 months). End of study: Will be 36 months after the last patient has been randomized.	**Phase:** III

Study design: This is a Phase III, double-blind, randomized multicenter study to compare the efficacy and to evaluate the safety and immunogenicity of HLX02 and European Union (EU)-sourced Herceptin® in patients with human epidermal growth factor receptor 2 (HER2)-positive, recurrent or previously untreated metastatic breast cancer. Eligible patients will be assessed centrally for HER2 status and the presence of at least one measurable target lesion before randomization. Patients will undergo a tumor assessment for evaluation of response according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) every 6 weeks up to 24 weeks (regardless of the number of cycles actually given); thereafter, assessments will be done every 9 weeks (after Cycles 11, 14, and 17) or earlier in the case of clinical signs of progression. All patients will remain in the study until Investigator-assessed disease progression, excessive toxicity, Investigator's judgment, withdrawal of consent, lost to follow-up, death, start of a new anticancer therapy, study termination by the Sponsor, or for a maximum of 12 months of treatment, whichever occurs first. After the Treatment Period (up to 12 months), patients will be referred to the local institution and will continue therapy in accordance with local practice. All patients will undergo a Safety Follow-up Visit 30 (±2) days after the last dose of study drug. Cardiac safety monitoring and immunogenicity testing will continue up to 12 months after randomization in all patients. Survival Follow-up will occur every 3 months until 12 months after randomization; thereafter, overall survival (OS) data will be collected by telephone call every 3 months for up to 36 months after randomization.

Objectives:

Primary:

To compare the efficacy of HLX02 versus EU-sourced Herceptin® in combination with docetaxel using overall response rate (ORR) up to Week 24 (ORR_{24}) after up to 8 cycles of treatment to demonstrate clinical bioequivalence.

Secondary:

- To evaluate the safety, tolerability, and immunogenicity of HLX02 and EU-sourced Herceptin® given in combination with docetaxel.

<table>
<tr><td colspan="2">

- To compare the efficacy of HLX02 versus EU-sourced Herceptin® in combination with docetaxel, in terms of duration of response (DoR), clinical benefit rate (CBR), disease control rate (DCR), progression-free survival (PFS) up to 12 months, and OS at 12, 24, and 36 months.
- To measure the exposure to trastuzumab following HLX02 or EU-sourced Herceptin®.

Exploratory:

- Exploratory population pharmacokinetic (PopPK) analysis.

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Rationale and methodology:

HLX02 is developed as a proposed biosimilar to Herceptin® to meet the need for alternatives to high-priced biologic agents in oncology treatments. This study will be conducted in patients with HER2-positive, recurrent or previously untreated metastatic breast cancer. The patients will be stratified for estrogen receptor/progesterone receptor (ER/PgR) status, prior neo-/adjuvant therapy with Herceptin®, and ethnicity (Asian and non-Asian), then randomized into 2 treatment arms in a 1:1 ratio to receive HLX02 or EU-sourced Herceptin® in combination with docetaxel according to the current standard of care. HLX02 or Herceptin® and docetaxel will be given once every 3 weeks for a maximum of 12 months. Tumor response for the primary efficacy analysis will be evaluated by central imaging review (CIR) for an independent, blinded determination of tumor response up to Week 24, after completion of up to 8 cycles of treatment. A CIR will occur at Screening to confirm eligibility and at Week 6, 12, 18, and 24 to compare the pattern of response. No CIR is required after Week 24. As of Cycle 9, patients will remain in the study and be followed every 9 weeks for other efficacy parameters such as DoR and PFS up to 12 months. Overall survival will be estimated at 12, 24, and 36 months.

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<tr><td>Planned number of patients:</td><td>A maximum of 304 patients will be enrolled in each arm to yield 289 evaluable patients per arm for the primary efficacy analysis in the intent-to-treat (ITT) population, accounting for a dropout rate of 5%.</td></tr>
<tr><td>Diagnosis:</td><td>Patients with HER2-positive, recurrent or metastatic breast cancer as centrally assessed by fluorescence in situ hybridization (FISH) or immunohistochemistry (IHC) who have not received prior systemic chemotherapy, biological or targeted agents for their recurrent or metastatic disease. Patients can have metastatic disease either at time of diagnosis, or after prior diagnosis of early breast cancer, provided neo-/adjuvant treatment containing trastuzumab and/or lapatinib was completed at least 12 months before the diagnosis of recurrent disease (local or metastatic) or neo-/adjuvant therapy containing a taxane (and no trastuzumab/lapatinib) was stopped at least 6 months before the diagnosis of recurrent (local or metastatic) disease. Neo-/adjuvant therapy with other cytotoxics only must have been stopped at least 4 weeks before randomization.</td></tr>
<tr><td>Investigational and comparator product, dose and route of administration:</td><td>Investigational product HLX02 (proposed biosimilar to trastuzumab) or comparator product EU-sourced Herceptin® (trastuzumab) will be administered intravenously as a loading dose of 8 mg/kg over 90 minutes on Day 1, Cycle 1, and then every 3 weeks for subsequent cycles at 6 mg/kg over 30-90 minutes (i.e. any duration between 30 and 90 minutes from Cycle 2 onwards) if the previous dose was well tolerated. If an infusion-related reaction (IRR) occurs, the infusion should be immediately interrupted (in patients with non-serious IRRs, at the Investigator's discretion, the infusion may be slowed) and the patient should be monitored until resolution of all symptoms. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol. Serious reactions must be treated with supportive therapy such as oxygen, beta-agonists, and corticosteroids. If a second episode of serious IRR occurs despite prophylactic use of steroids (see section on prophylactic drugs below) treatment will be permanently discontinued. Treatment with HLX02 or</td></tr>
</table>

	Herceptin® will continue for a maximum of 12 months, or until Investigator-assessed disease progression, excessive toxicity, Investigator's judgment, withdrawal of consent, lost to follow-up, death, start of a new anticancer therapy, or study termination by the Sponsor, whichever occurs first. HLX02 or Herceptin® administration may be delayed but no dose reduction is allowed. If a patient misses a dose of HLX02 or Herceptin® by less than 1 week after the planned date, the usual maintenance dose (6 mg/kg) should be given as soon as possible. Do not wait until the next planned cycle. If a patient misses a dose of HLX02 or Herceptin® for ≥1 week (i.e. the 2 sequential administrations are given ≥4 weeks apart), a re-loading dose of HLX02 or Herceptin® (8 mg/kg) should be given. Subsequent maintenance HLX02 or Herceptin® doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later. If re-loading is required, docetaxel administration (at the dose that was last tolerated) will be restarted on the same day as the re-loading dose, to coincide with the start of a new cycle. If a patient has a study drug interruption ≥9 weeks for a trastuzumab-related toxicity, they will be discontinued from the study.
Associated product:	**Docetaxel** will be administered as an intravenous dose of 75 mg/m² over 60 minutes according to prescribing information. Patient weight must be monitored before any subsequent administration and furosemide (or equivalent diuretic) will be given orally in the case of fluid retention. Premedication with steroids (see section on prophylactic drugs below) will be given. If a severe IRR occurs, docetaxel will be permanently discontinued. The first dose of docetaxel will be given on Day 2 (HLX02 or Herceptin® given on Day 1). If well tolerated, as determined by the Investigator, then the same dose will be given every 3 weeks on Day 1 of each subsequent cycle always starting 60 minutes after the end of the HLX02 or Herceptin® infusion. Note: At the Investigator's discretion, the dose of docetaxel can be increased to 100 mg/m² in patients who have tolerated at least 1 administration of 75 mg/m² without febrile neutropenia, Grade 4 neutropenia >5 days, ANC <100/μL more than 1 day, or any non-hematological toxicities of > Grade 2. If treatment is withheld for more than 1 week for granulocyte recovery, or if a febrile neutropenic episode occurs at any time during therapy, prophylactic G-CSF will be administered with all subsequent cycles. Prophylactic use of G-CSF **before the first cycle** is not allowed unless the patient had prior severe neutropenia during neo-/adjuvant therapy. At any time during the Treatment Period, docetaxel should be discontinued for progressive disease or unacceptable toxicity. After Cycle 8, continuation of docetaxel treatment is at the discretion of the Investigator. At the time docetaxel is permanently discontinued for any reason other than disease progression, the patient can continue on Herceptin® or HLX02 alone if still benefiting from the treatment.
Prophylactic drugs:	All patients treated with docetaxel will be given either oral or intravenous dexamethasone as follows: Oral: on Day 2 of Cycle 1, patients will be given 7.5-8 mg (depending on the available tablet dosage form) dexamethasone orally at 24 hours (about the same time as the HLX02 or Herceptin® infusion on Day 1) and 12 hours before the start of the docetaxel infusion. In subsequent cycles (Cycle 2 onwards), administration of 7.5-8 mg dexamethasone orally will occur at 24 hours and 12 hours before the HLX02 or Herceptin® infusion, followed

	1 hour later by the docetaxel infusion. After the docetaxel infusion, 7.5-8 mg dexamethasone should be given twice daily for a further 48 hours. Intravenous: on Day 2 of Cycle 1, patients will be given 20 mg dexamethasone intravenously approximately 30 minutes before the start of the docetaxel infusion. In subsequent cycles (Cycle 2 onwards), patients will be given 20 mg dexamethasone intravenously after the HLX02 or Herceptin® infusion and before the docetaxel infusion. After the docetaxel infusion, 7.5-8 mg dexamethasone should be given twice daily for 48 hours.

Key inclusion criteria:

- Male or female ≥18 years of age on day of signing the informed consent form (ICF)
- Histologically or cytologically confirmed adenocarcinoma of the breast
- Recurrent disease not amenable to curative surgery or radiation therapy, or metastatic disease with an indication for a taxane-containing therapy
- Availability of formalin-fixed paraffin-embedded tissue block from the primary tumor, or a metastatic lesion, to confirm HER2-positivity by the central laboratory, based on FISH amplification ratio ≥2.0 or IHC score 3+, and for hormone status (ER/PgR) determination (local or central laboratory). If not possible, a fresh biopsy is required
- No prior systemic anticancer agent such as chemotherapy, biological or targeted agent for metastatic disease with the exception of hormonal therapy, which must be stopped at least 2 weeks before randomization. Use of herbal remedies or traditional Chinese medicines for anticancer, hematologic or liver function, or anti-infective treatment must be stopped at the time of the ICF signature (at least 2 weeks before randomization)
- For patients with recurrent disease, prior neo-/adjuvant therapy containing trastuzumab and/or lapatinib must have been stopped at least 12 months before the diagnosis of recurrent (local or metastatic) disease (i.e. a disease-free interval of ≥12 months). If trastuzumab/lapatinib was not used, prior neo-/adjuvant therapy with a taxane must have been stopped at least 6 months before the diagnosis of recurrent (local or metastatic) disease (i.e. a disease-free interval of ≥6 months). If only other cytotoxics were given, they must be stopped at least 4 weeks before randomization. Any hormonal therapy must be stopped at the time of the ICF signature (at least 2 weeks before randomization)
- Measurable disease (at least one measurable target lesion assessed by CIR; bone-only or central nervous system [CNS]-only metastases are not allowed)
- Eastern Cooperative Oncology Group performance status of 0-1
- Left ventricular ejection fraction (LVEF) within institutional range of normal at baseline (within 42 days before randomization) as determined by either echocardiography (ECHO) or multigated acquisition (MUGA) scan
- Adequate hematologic, hepatic and renal function
- Estimated life expectancy ≥3 months
- Female patients are eligible to enter and participate in the study if they are of:
  - Non-childbearing potential
  - Childbearing potential, have a negative serum pregnancy test at Screening (within 7 days of the first investigational/comparator product administration), are not breast feeding, and use highly-effective or acceptable contraceptive measures before study entry and throughout the study until 7 months after the last investigational/comparator product administration
- Male patients with partners of childbearing potential are eligible to enter and participate in the study if they are willing to use highly-effective or acceptable contraceptive measures before study entry and throughout the study until 7 months after the last investigational/comparator product administration

Key exclusion criteria:

- Previously- or currently-treated (systemic chemotherapy, biological, or targeted agent, or any other anticancer agent) metastatic breast cancer with the exception of hormonal therapy
- Known brain metastasis or other CNS metastasis that is either symptomatic or untreated. Central nervous system metastases that have been treated by complete resection and/or radiotherapy demonstrating stability or improvement are not an exclusion criterion provided they are stable as shown by computed tomography (CT) scan for at least 4 weeks before Screening without evidence of cerebral edema and no requirements for corticosteroids or anticonvulsants
- Underlying medical conditions or current severe, uncontrolled systemic disease that, in the Investigator's opinion, will make the administration of study drug hazardous. A major surgical procedure (defined as a procedure that would require more than 3 weeks without study treatment) within 4 weeks prior to enrolment or anticipation of the need for major surgery during the course of study
- Current uncontrolled hypertension (systolic >150 mmHg and/or diastolic >100 mmHg) or unstable angina
- History of chronic heart failure of any New York Heart Association criteria, or left ventricular hypertrophy. Current serious cardiac arrhythmia requiring treatment (except atrial fibrillation, paroxysmal supraventricular tachycardia) or clinically significant conduction defects as seen on electrocardiogram. History of myocardial infarction within 6 months of randomization. History of LVEF decline to below 50% during or after prior trastuzumab neo-adjuvant or adjuvant therapy. Significant cardiac murmurs either on examination or ECHO
- History of prior exposure to doxorubicin >360 mg/m² (or equivalent)
- Use of oral, injected or implanted hormonal methods of contraception
- Known hypersensitivity to any of the study drugs
- Residual non-hematologic toxicity ≥ Grade 2 from prior therapy.

Criteria for evaluation:

Primary Efficacy Endpoint:

- ORR_{24}, calculated as the proportion of patients with a best response of complete response (CR) or partial response (PR) from first assessment up to Week 24 according to RECIST 1.1. The response does not need to be confirmed. Overall tumor response will be assessed by blinded, independent CIR according to RECIST 1.1

Secondary Efficacy Endpoints:

- ORR at Week 6, 12, 18, and 24 by CIR
- DoR, defined as the time from first documentation of CR or PR to the first documentation of progression. After Week 24, assessments are made by the Investigator
- DCR, defined as the proportion of patients who achieve CR, PR, or stable disease (SD) of at least 12 weeks
- CBR, defined as the proportion of patients who achieve CR, PR, or durable SD (SD ≥24 weeks)
- PFS up to 12 months, defined as the probability of being alive without documented progression up to 12 months after randomization, calculated using the Kaplan-Meier method
- Overall survival at 12, 24, and 36 months, defined as the probability of being alive 12, 24, and 36 months after randomization, calculated using the Kaplan-Meier method

Pharmacokinetic (PK) and Immunogenicity Data:

In all patients, PK blood samples to determine serum trastuzumab concentrations will be collected prior to infusion at Cycle 1 (at the time of blood sampling for assessment of hematology and level of HER2 shed antigen), and starting at Cycle 3, prior to infusion every 3 cycles (approximately every 9 weeks), at the same time as sample collections to assess for the presence of anti-drug antibodies (ADA)/neutralizing ADA (NADA) while on treatment with HLX02 or Herceptin®.

Additional blood samples for the determination of trastuzumab in serum will be collected in all enrolled patients at the following time points:

- Cycle 1, Day 1, at the end of infusion
- Cycles 4 and 8, prior to infusion (at the time of blood sampling for assessment of hematology)
- Cycle 8, Day 1, at the end of infusion

Blood samples to test for the baseline level of HER2 shed antigen and for antibodies against trastuzumab (ADA/NADA) must be collected in all patients within 7 days prior to the first administration of study drug (Screening). In addition to the on-treatment ADA/NADA samples described above, a blood sample will also be taken at the Safety Follow-up Visit to assess for the presence of ADA/NADA (along with blood sampling for routine laboratory tests).

Safety:

Safety and tolerability of HLX02 or Herceptin® and docetaxel assessed throughout the study by the incidence, severity and causality of serious adverse events (SAEs), adverse events (AEs) and adverse events of special interest (AESI), coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03). Patients will be monitored by physical examination, vital signs, electrocardiograms, and laboratory tests classified for severity using NCI CTCAE v4.03. Cardiac function will be evaluated by ECHO or MUGA scan using the same method throughout the entire study period (ECHO is preferred). Cardiac assessments will be performed after every 3 cycles (within 3 days of the start of Cycles 4, 7, 10, etc.) or more frequently if clinically indicated; at the Safety Follow-up Visit; and during Survival Follow-up (every 3 months until 12 months after randomization if study treatment has been discontinued).

Statistical methods:

Sample Size determination using the difference in proportion of patients with ORR_{24} in the ITT and per-protocol (PP) populations:

The difference in rate of ORR (Herceptin®- control) and its two-sided 95% confidence interval (CI) was calculated by pooling the results of the subgroup of patients with HER2-positive tumors defined as FISH positive or IHC 2+ and 3+, from 2 published randomized studies comparing ORR following treatment with Herceptin® + paclitaxel or equivalent versus paclitaxel or equivalent alone (Genentech, 2010, Table 9; Marty et al, 2005, Table 2). Using the Der Simonian-Laird estimate random effect model (Der Simonian and Laird, 1986), the difference in ORR and its 95% CI was estimated to be 0.2493 [0.1579; 0.3407]. The metabin function of the meta library of the R language (R Core Team, 2012) was used to implement this estimate. An equivalence limit marginally tighter than the lower bound of this CI is used as the criterion of equivalence: [-0.1350; 0.1350]. Given the published ORRs for ITT populations in Marty et al (2005: 61%), CLEOPATRA (Baselga et al, 2012: 69%), and HERITAGE (Hope et al, 2016: 64%) trials, a conservative rate of 60% ORR_{24} was assumed for the ITT population. A sample size of 289 evaluable patients per arm was calculated to yield 84% power to show equivalence using the above equivalence limits [-0.1350; 0.1350] with the two-sided 95% CI for the difference in ORR_{24} HLX02-Herceptin® in the ITT population. Assuming a 5% dropout rate, the number of patients required to be randomized is approximately 304 per arm. Swain et al (2015) has approximately 8% of patients discontinuing who would be excluded from a PP population. Based on this, a 10% drop in patients is assumed in the PP population, compared to the ITT population, making a total of approximately 15% dropout in the PP population. It is assumed that 3% of ITT patients with ORR fail to be included in the PP population (e.g. due to protocol deviations other than early discontinuation). Under these assumptions the denominator for ORR will decrease by 10%, compared to that of the ITT population, but the number of ORRs will decrease by only 3%. It is thus assumed there will be a higher rate of 65% ORR_{24} in the PP population. With these assumptions, 304 patients per arm will yield a sample size for the PP population of approximately 258 and the study will have 80% power to show equivalence in the PP population.

A blinded sample size re-estimation procedure is planned after the primary efficacy data at Week 24 are available in the first 300 patients. A Data Monitoring Committee will oversee the re-estimation procedure as well as review safety data and monitor the overall conduct of the study.

Efficacy: The primary endpoint will be the ORR_{24}. Equivalence will be concluded if the two-sided 95% CI of the difference of the 2 proportions is completely contained within the interval [-0.1350; 0.1350]. Two-sided 95% CIs for the difference between the 2 treatment arms in ORR_{24} will be presented, controlling for randomizing stratification factors using Mantel-Haenszel weights for the strata. The ITT population will be considered the primary population for the efficacy analyses. Repeat analyses using the PP population will explore robustness of results; the robustness to missing data of conclusions from the ITT analysis will be assessed via sensitivity analyses. Overall objective response at Week 6, 12, 18, and 24 by CIR will be analyzed in a similar way to that of the primary endpoint to show the pattern of response. For time-to-event secondary endpoints (DoR, PFS up to 12 months and OS at 12, 24, and 36 months), Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics (i.e. probability of being event-free) and corresponding two-sided 95% CIs. The CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980). The estimate of the standard error will be computed using Greenwood's formula. A Cox model will be used to compare the hazard ratio (HR). The point estimates and two-sided 95% CIs of the HR will be reported. Binary secondary endpoints (ORR at other time points, DCR and CBR) will be analyzed in a similar way to that of the primary endpoint but ratios will be estimated, controlling for randomizing stratification factors through a log binomial model.

Safety: Descriptive statistics will be used to present SAEs, AEs and AESI and other safety variables.

Pharmacokinetics: Trastuzumab concentrations in serum will be summarized descriptively by study population, treatment and scheduled collection time. Exposure to trastuzumab will be further evaluated with respect to specific disease characteristics such as baseline levels of shed antigen. Additional PopPK modeling and/or correlation between trastuzumab exposure and response (safety, immunogenicity and/or efficacy) data may be evaluated separately, as appropriate. If performed, a separate analysis plan will be prepared and results will be reported separately from the Clinical Study Report.

Database Locks: The first database lock will occur once response assessment data up to Week 24 are available for all patients, at which time the designated unblinded study team will conduct analyses on the primary efficacy data, as well as PK, safety/immunogenicity and survival data, up to Week 24. All Investigators, site teams, and patients will remain blinded until the end of the Treatment Period (up to 12 months after the last patient randomized), which is when the second database lock will occur. At that time, analyses will be conducted on all efficacy, PK, safety and survival data over 12 months for all patients. The final database lock will occur 36 months after last patient randomized in order to report OS.

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody(ies)
AE	Adverse event
AESI	Adverse event(s) of special interest
ALK	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPPT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
CAP	College of American Pathologists
CBR	Clinical benefit rate
CHF	Congestive heart failure
CI	Confidence interval
CIR	Central imaging review
CNS	Central nervous system
CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography (scan)
DCR	Disease control rate
DMC	Data Monitoring Committee
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ER	Estrogen receptor
EU	European Union

Abbreviation	Definition
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV-DNA	Hepatitis B virus-deoxyribonucleic acid
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition (scan)
NADA	Neutralizing anti-drug antibody(ies)
NCI-CTCAE v4.03	National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03
NYHA	New York Heart Association
ORR	Overall response rate
ORR_{24}	Overall response rate at 24 weeks
OS	Overall survival
PET	Positron emission tomography (scan)

Abbreviation	Definition
PFS	Progression-free survival
PgR	Progesterone receptor
PK	Pharmacokinetic
PopPK	Population pharmacokinetic
PP	Per-protocol
PPT	Partial thromboplastin time
PR	Partial response
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamate-pyruvate transaminase
SOP	Standard operating procedures
ULN	Upper limit of normal

2.0 INTRODUCTION

2.1 Background Information

Breast cancer is the most common cancer in women, with a global incidence of more than 1.5 million patients and a mortality rate of approximately 500,000 deaths per year.[1] In western countries, metastatic breast cancer makes up less than 1% of all cancers in men and its incidence seems to vary according to different geographical areas and ethnic groups.[2] Although rare, metastatic breast cancer in men appears to be increasing as reported by the Surveillance, Epidemiology and End Results Program of the National Cancer Institute, and reviewed by the United Kingdom Association of Cancer Registries.[3]

Of the total number of patients diagnosed with breast cancer, 20% to 25% have tumors that exhibit human epidermal growth factor receptor 2 (HER2) protein overexpression or gene amplification. HER2 belongs to a family of 4 transmembrane receptor tyrosine kinases that mediate the growth, differentiation and survival of cells.[4,5] HER2 overexpression is associated with aggressive tumor biology and with poor clinical outcomes compared with tumors that do not have HER2 overexpression.[6]

Trastuzumab is a humanized monoclonal antibody that specifically binds to the extracellular parts of HER2 to competitively inhibit the receptor function, resulting in the inhibition of tumor cell growth (see the latest Investigator's Brochure for HLX02). Trastuzumab was initially developed by Genentech and Roche and approved by the United States' Food and Drug Administration in 1998 with the brand name of Herceptin®. Herceptin® demonstrated clinical activity in patients with HER2-overexpressing metastatic breast cancer, both as single-agent therapy and in combination with chemotherapy. A pivotal Phase III study demonstrated that the combination of trastuzumab and different chemotherapies (including paclitaxel) significantly prolonged time to progression and overall survival (OS) compared with chemotherapy alone in patients with HER2-overexpressing metastatic breast cancer.[7] In another randomized Phase II study, the addition of trastuzumab to docetaxel showed improved response rate, time to progression, and OS compared with docetaxel alone.[8] Herceptin® was also approved by the European Medicines Agency (EMA) in 2006 and the Chinese Food and Drug Administration in 2002 for use as monotherapy in patients with HER2-positive metastatic breast cancer who have received one or more chemotherapy regimens and in combination with a taxane for metastatic disease. More recently, Herceptin® was approved in the adjuvant setting by all Agencies (for more details see the latest Investigator's Brochure for HLX02).

Shanghai Henlius Biotech, Inc. (the Sponsor) is currently developing a recombinant anti-HER2 humanized monoclonal antibody for injection (HLX02) as a proposed biosimilar

drug to trastuzumab (Roche Herceptin®), formulated as 150 mg/vial. Since demonstration of similarity in quality and non-clinical study is a prerequisite for clinical development, the Sponsor has conducted a number of studies on the substance, formulation, and technology of HLX02, as well as structure confirmation, batch development and quality comparisons with the original drug, Herceptin®. Drug stability and packaging have also been tested. Comparison of the structural characteristics, physiochemical properties and biological activities between HLX02 and Herceptin® was performed in accordance with EMA guidelines (EMEA/CHMP/BWP/247713/2012). A series of in vitro and in vivo studies was performed in order to demonstrate similarity between HLX02 and Herceptin®. A risk-based approach was taken to the non-clinical evaluation of HLX02 based on the EMA guideline (EMA/CHMP/BMWP/403543/2010). Comparison-based pre-clinical studies on the pharmacology, pharmacodynamics, pharmacokinetic (PK) profile and toxicology of HLX02 have shown that the drug shares a high similarity with Herceptin® (see the latest Investigator's Brochure for HLX02).

As a second step in the development of HLX02 as a proposed biosimilar of trastuzumab, a Phase I clinical study comparing HLX02 with European Union (EU)-sourced and China-sourced Herceptin® is currently being conducted in healthy volunteers in China. The study is conducted in accordance with the EMA guidelines for monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

2.2 Rationale

HLX02 is being developed as a proposed biosimilar to the approved drug, Herceptin® to meet the need for an alternative to this high-priced biologic agent. The efficacy and safety of trastuzumab have already been demonstrated during the development of Herceptin®. The objective of this Phase III study is to compare the efficacy and to evaluate safety and immunogenicity of HLX02 + docetaxel and EU-sourced Herceptin® + docetaxel in patients with HER2-positive, recurrent or previously untreated metastatic breast cancer. Blood samples will be collected to measure trastuzumab concentrations.

This Phase III study will be performed in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), in accordance with the EMA guidelines for monoclonal antibodies and with applicable local regulatory requirements in other participating countries.

2.3 Hypothesis

The primary hypothesis for the primary efficacy analysis is that HLX02 is neither inferior nor superior to Herceptin® based on a pre-specified equivalence margin.

2.4 Risk Assessment

Clinical testing has shown that the benefit of Herceptin® is greatest in patients with tumors strongly overexpressing HER2, i.e. in tumors graded 3+ by immunohistochemistry (IHC), and/or with HER2 gene amplification, as determined by fluorescence in situ hybridization (FISH).[9]

In the reference study, using the same regimen as the one proposed for this biosimilar study, a total of 186 patients were randomized to receive either trastuzumab + docetaxel or docetaxel alone.[8] The addition of trastuzumab to 100 mg/m^2 docetaxel for at least 6 cycles resulted in superior clinical efficacy with improved overall response rate (ORR; 61% versus 34%; P = 0.0002), OS (median, 31.2 versus 22.7 months; P = 0.0325), time to progressive disease (median, 11.7 versus 6.1 months; P = 0.0001), time to treatment failure (median, 9.8 versus 5.3 months; P = 0.0001), and duration of response (median, 11.7 versus 5.7 months; P = 0.009). There was little difference in the number and severity of adverse events (AEs) between the groups. Grade 3 to 4 neutropenia was seen more commonly with the combination (32%) than with docetaxel alone (22%), and there was a slightly higher incidence of febrile neutropenia in the combination group (23% versus 17%). More patients in the combination group had left ventricular ejection fraction (LVEF) decreases ≥15% compared with the docetaxel alone group (17% versus 8%), and 1 patient (1%) in the combination group experienced symptomatic congestive heart failure (CHF).[8]

Based on these results, trastuzumab is considered to be well tolerated in combination with standard chemotherapy for metastatic breast cancer, provided that adequate patient selection is made particularly in terms of cardiac baseline conditions. Indeed the most significant AE observed in patients who receive trastuzumab is cardiac dysfunction, reflected by asymptomatic decreases in LVEF and, less frequently, by clinically symptomatic CHF. Risk factors for cardiac failure include co-administration with anthracycline-based chemotherapy, increasing age, a declining LVEF during treatment to below the lower limit of normal, and the use of anti-hypertensive medications.[9] In our well selected patient population undergoing proper surveillance, the benefit of adding trastuzumab largely exceeds the risk of cardiac AEs. Other potential risks, given the safety profile of Herceptin®, are pulmonary events, hypersensitivity reactions or infusion-related reactions (IRR), and immunogenicity.

3.0 STUDY OBJECTIVE(S)

3.1 Primary Objective

The primary objective of the study is to compare the efficacy of HLX02 versus EU-sourced Herceptin® in combination with docetaxel using ORR up to Week 24 (ORR_{24}) after up to 8 cycles of treatment to demonstrate clinical bioequivalence.

3.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the safety, tolerability, and immunogenicity of HLX02 and EU-sourced Herceptin® given in combination with docetaxel.
- To compare the efficacy of HLX02 versus EU-sourced Herceptin® in combination with docetaxel, in terms of duration of response (DoR), clinical benefit rate (CBR), disease control rate (DCR), progression-free survival (PFS) up to 12 months, and OS at 12, 24, and 36 months.
- To measure the exposure to trastuzumab following HLX02 or EU-sourced Herceptin®.

3.3 Exploratory Objective

- Exploratory population pharmacokinetic (PopPK) analysis.

4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This is a Phase III, double-blind, randomized, multicenter study to compare the efficacy and to evaluate the safety and immunogenicity of HLX02 and EU-sourced Herceptin® in patients with HER2-positive, recurrent or previously untreated metastatic breast cancer. A maximum of 608 patients with a confirmed measurable target lesion by CIR will be enrolled. Patients will be stratified for estrogen receptor/progesterone receptor (ER/PgR) status, prior neo-/adjuvant therapy with Herceptin®, and ethnicity (Asian and non-Asian), then randomized into 2 treatment arms in a 1:1 ratio to receive HLX02 or EU-sourced Herceptin® in combination with docetaxel according to the current standard of care. HLX02 or EU-sourced Herceptin® will be administered intravenously, initially at a loading dose of 8 mg/kg on Day 1, Cycle 1 then at a dose of 6 mg/kg once every 3 weeks in 3-weekly cycles for up to a maximum of 12 months. Docetaxel 75 mg/m^2 will be administered intravenously (after HLX02 or EU-sourced Herceptin®) once every 3 weeks for at least 8 cycles and thereafter at the Investigator's discretion for up to a maximum of 12 months.

The evaluation of tumor response will be measured according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). The Investigator will assess the response every 6 weeks up to 24 weeks (regardless of the number of cycles actually given); thereafter assessments will be done every 9 weeks (after Cycles 11, 14, and 17) or earlier in the case of clinical signs of progression. Tumor response for the primary efficacy analysis will be evaluated by central imaging review (CIR) for an independent, blinded determination of tumor response up to Week 24, after completion of up to 8 cycles of treatment. A CIR will occur at Screening to confirm eligibility and at Week 6, 12, 18, and 24 to assess the pattern of response; no CIR is required after Week 24 (see Section 6.1.1.2). As of Cycle 9, patients will remain in the study and be followed every 9 weeks for other efficacy parameters such as DoR and PFS up to 12 months, and OS at 12, 24, and 36 months. All patients will remain in the study until Investigator-assessed disease progression, excessive toxicity, Investigator's judgment, withdrawal of consent, lost to follow-up, death, start of a new anticancer therapy, study termination by the Sponsor, or for a maximum of 12 months of treatment, whichever occurs first. At the end of the Treatment Period (up to 12 month), patients will be referred to the local institution and will continue therapy in accordance with local practice. All patients will undergo a Safety Follow-up Visit 30 (±2) days after the last dose of study drug (maximum of 17 cycles). Cardiac safety monitoring and immunogenicity testing will continue up to 12 months after randomization in all patients. Survival Follow-up will occur every 3 months until 12 months after randomization; thereafter, survival data will be collected by telephone call every 3 months for up to 36 months after randomization.

Extended PK samples will be collected in all patients to further support the Phase I data obtained from healthy volunteers. Compliance with PK sample collections as well as recording of PK sampling information on the patients' electronic case report form (eCRF) will be closely monitored. As part of the extended sample collections, trough trastuzumab levels (defined as PK samples collected at the time of the laboratory tests within a maximum of 3 days prior to Day 1 of the cycle) will be correlated with baseline levels of the circulating extracellular domain of the HER2 receptor (shed antigen).

Collection of PK samples at the same time as the scheduled anti-drug antibody (ADA)/neutralizing ADA (NADA) assessment will occur in all patients to fully measure the effect of potential ADA formation on trastuzumab exposure for both HLX02 and EU-sourced Herceptin®. As of Cycle 3, blood sampling for ADA/NADA assessment will continue every 3 cycles (approximately every 9 weeks) up to 12 months.

A maximum of 304 patients will be enrolled in each arm to yield 289 evaluable patients for the primary efficacy analysis in the intent-to-treat (ITT) population accounting for a dropout rate of 5%. Patients will be enrolled from approximately 83 centers worldwide.

End of study will occur 36 months after the last patient is randomized.

The study design is presented in Figure 4-1 and the schedule of events is presented in Table 4-1.

Figure 4-1 Schematic of Study Design for Protocol HLX02-BC01

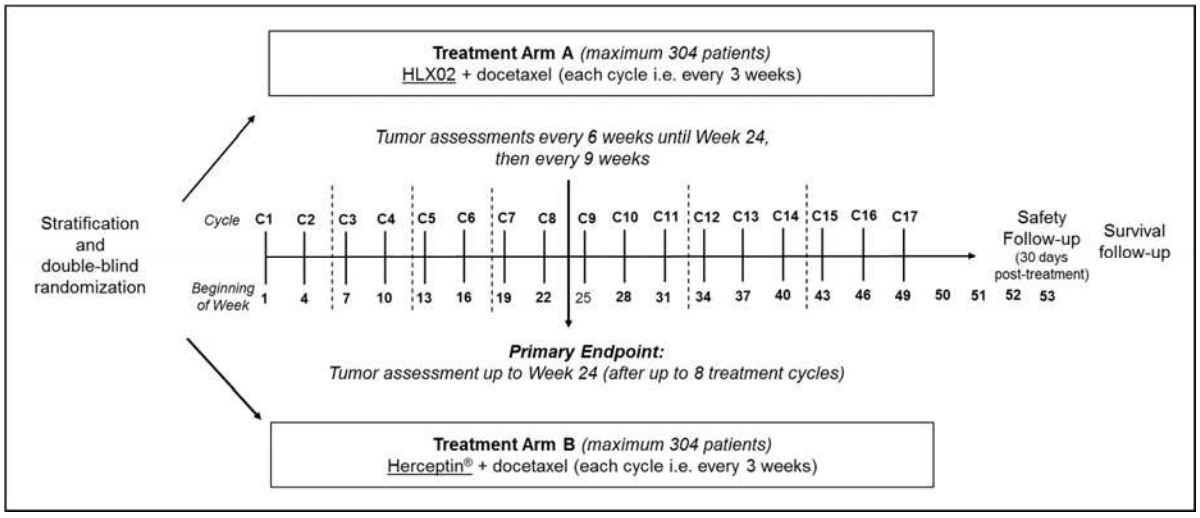

Table 4-1 Schedule of Events

Assessments	Screening Period (baseline)[1]	Randomization	Treatment Period *(each cycle is 3 weeks)*		Safety Follow-up[3]	Survival Follow-up[4]
			---------- 12 months (52 weeks) ----------			*---- 24 months ----*
			HLX02 or Herceptin + Docetaxel[2]			
Days	**-28 to -1**		**Every Cycle Day 1**	**Every Cycle Day 8**	**30 days post-treatment**	**Every 3 months**
Visit Window (days)	**-**		**±3**	**±1**	**±2**	**±7**
Informed Consent[5]	X		-	-	-	-
Inclusion/Exclusion criteria	X		-	-	-	-
Hormone and HER2 status[6]	X		-	-	-	-
Demographics/Medical history[7]	X		-	-	-	-
Physical examination/Vital signs[8]	X		X	-	X	-
Weight[8]	X		X			
ECOG performance status (see Appendix 3)	X		-	-	X	-
12-lead ECG[9]	X		X	-	X	-
Pregnancy serum test[10]	X		X (every 3 cycles)	-	X	-
HIV, hepatitis B and C[11]	X		-	-	-	-
LVEF (ECHO or MUGA scan)[12]	X		X (every 3 cycles)	-	X[12]	-
HLX02 or Herceptin®	-		X	-	-	-
Docetaxel	-		X[13]	-	-	-
Adverse events[14]	X		X		X	-
Tumor assessment (imaging)[15]	X[15]		Week 6, 12, 18, 24 then every 9 weeks (after Cycles 11, 14, 17)		X	-
Concomitant medications	X		X	X	X	-
Hematology[16]	X		X	X[16]	X	-
Serum chemistry panel and coagulation[16]	X		X	-	X	-
Urinalysis (including pregnancy test)[17]	X		X	-	X	-

Assessments	Screening Period (baseline)[1]	Randomization	Treatment Period *(each cycle is 3 weeks)*		Safety Follow-up[3]	Survival Follow-up[4]
			---------- 12 months (52 weeks) ----------			*---- 24 months ----*
			HLX02 or Herceptin + Docetaxel[2]			
Days	**-28 to -1**		**Every Cycle Day 1**	**Every Cycle Day 8**	**30 days post-treatment**	**Every 3 months**
Visit Window (days)	**-**		**±3**	**±1**	**±2**	**±7**
Pharmacokinetic blood sampling[18]			X[18]		-	-
Serum test for ADA/NADA[19]	X		At Cycle 3, then every 3 cycles (approx. every 9 weeks)		X	-
Overall survival			Every 3 months			X

ADA = anti-drug antibodies; AE = adverse event; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiography; ECOG = Eastern Corporative Oncology Group; eCRF = electronic case report form; ER = estrogen receptor; FISH = fluorescence in situ hybridization; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV-DNA = hepatitis B virus deoxyribonucleic acid; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; IHC = immunohistochemistry; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NADA = neutralizing anti-drug antibodies; NCI-CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events; OS = overall survival; PgR = progesterone receptor; PK = Pharmacokinetic; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RNA = ribonucleic acid.

1. During the Screening period, routine laboratory tests (serum chemistry, hematology, immunogenicity test, and urinalysis) will be performed within 7 days prior to enrollment.
2. If docetaxel is permanently discontinued for any reason other than disease progression, the patient can continue on HLX02 or Herceptin® alone if the patient is still benefiting from the treatment.
3. The Safety Follow-up Visit will take place 30 (±2) days after the last administration of docetaxel and/or HLX02 or Herceptin®, whichever occurs last at the end of the 12-month Treatment Period, or earlier for any reason except withdrawal of consent.
4. Survival Follow-up will occur every 3 months, at the time of tumor assessment during the Treatment Period, up to 12 months after randomization; thereafter survival data will be collected by telephone call up to 36 months after randomization.
5. Signed informed consent form must be obtained prior to performing any protocol-specific procedure.
6. Hormone status (ER and PgR) determined by IHC at a local or central laboratory. For HER2 status, a previous local IHC test with a score of IHC 2+ or 3+ can be used as a Prescreening evaluation but will not be sufficient for enrollment. To be eligible, a patient must be confirmed as HER2-positive by a central laboratory using FISH (amplification ratio ≥2.0) or IHC (score of 3+) test. Patients with a previous local IHC score of 2+ must be tested centrally by FISH and those patients with a previous local IHC score of 3+ must be confirmed centrally by IHC.
7. Complete medical history including breast cancer and significant diseases, demographics (i.e. age, sex, race and ethnicity), and all medications taken during the 90 days before randomization including anticancer therapies. Prior anticancer treatments, including neo-/adjuvant therapy and hormone therapy, should also be recorded on the eCRF.
8. Vital signs include temperature, pulse, respiratory rate and blood pressure. Height and body weight will be measured at baseline. **Weight will also be measured on Day 1 (maximum 3 days before Day 1) of every treatment cycle** for confirmation of body surface area calculation (to be calculated each cycle by the Interactive Web/Voice Response System). The dose will be adjusted only if the patient's weight changes by more than ±10% from baseline. Symptom-directed physical examination will be performed every cycle with particular attention to cardiovascular signs and symptoms.

9. 12-lead ECG assessments will be performed while the patient is in supine or semi-recumbent position after resting for 5 minutes. Screening ECG should be performed within 5 days before Day 1. An ECG will be repeated at every cycle (**within 3 days prior to Cycles 2, 3, etc.**) at the time of the LVEF assessment (where applicable), and at the Safety Follow-up Visit.
10. Women of childbearing potential must have a negative serum pregnancy test at Screening (within 7 days of the first administration of HLX02 or Herceptin®); then a serum pregnancy test should be done during the Treatment Period **within 3 days prior to Cycles 3, 6, 9, etc.** (every third cycle), and at the Safety Follow-up Visit At any time point, if a urine test (see Footnote 17) is found to be positive, the pregnancy must be confirmed with a serum test via the local laboratory.
11. Blood samples will be analyzed at the local laboratory for HBcAb and HBsAg (if HBcAb or HBsAg positive, HBV-DNA should be tested), hepatitis C (hepatitis C antibody and/or hepatitis C virus RNA should be tested), and HIV.
12. LVEF will be calculated to monitor cardiac safety at Screening within 42 days before randomization, after every 3 cycles (**within 3 days prior to Cycles 4, 7, 10, etc.**), or more frequently if clinically indicated, at the Safety Follow-up Visit, and during Survival Follow-up (**every 3 months until 12 months after randomization if study treatment has been discontinued)**. The same method of assessment, either ECHO (preferred) or MUGA scan must be used throughout the entire study period. Patients for whom study drug was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 3 months until the LVEF values return to ≥50%.
13. The first dose of docetaxel will be administered on **Day 2, Cycle 1**. Subsequent doses will be administered on Day 1 of each cycle **always 60 minutes after** the administration of HLX02 or Herceptin®. Continuation of docetaxel after Cycle 8 is at the Investigator's discretion. Treatment will continue up to a maximum of 12 months (17 cycles).
14. All AEs (including abnormal laboratory values that translate into clinical symptoms), graded as per NCI-CTCAE v4.03, are to be collected from the time of signed informed consent on a continuous reporting basis. All AEs, whether gradable by NCI-CTCAE or not, will be evaluated for seriousness. Cardiac AEs will be collected up to 12 months after randomization in line with LVEF calculations.
15. Tumor assessments (based on RECIST 1.1) must be performed at Screening (baseline), at Week 6, 12, 18, and 24 (regardless of the number of cycles actually given), and then every 9 weeks (between Days 15-21 after Cycles 11, 14, and 17) by CT or MRI, using the same method throughout the whole study. At the Safety Follow-up Visit, a tumor measurement must be repeated unless the patient has undergone a CT scan within the last 4 weeks. Bone scans or X-rays and brain CT scan/MRI should be performed at Screening if clinically indicated and during the Treatment Period as clinically indicated. Positron emission tomography scans are not accepted for assessment of efficacy. At baseline CT/MRI of the chest and abdomen (including liver, spleen, and adrenals) must be performed, and pelvis if clinically indicated; then the assessment will be done according to initial findings and emerging clinical symptoms. For patients who discontinue study drug for reasons other than death, Investigator-assessed disease progression, excessive toxicity, or withdrawal of consent, efforts should be made to continue to perform scheduled tumor assessments for up to a maximum of 12 months after randomization or until patient death, Investigator-assessed disease progression, withdrawal of consent, or start of a new anticancer therapy. **Note: The tumor measurement at Screening will undergo central imaging review to confirm eligibility before the patient can be randomized**.
16. Routine laboratory tests (hematology [complete blood count with differential], serum chemistry, coagulation, and urinalysis) will be performed by the local laboratory. At Screening, eligibility must be confirmed by a test collected no more than 7 days prior to Day 1 and for subsequent cycles, laboratory tests must be performed **within a maximum of 3 days prior to Day 1 of each cycle** (i.e. before HLX02 or Herceptin® administration). The results must be available before each study drug infusion. An additional hematology blood test will be performed on **Day 8 of each cycle,** either at the study center or another hospital, during the period docetaxel is administered but not during the period study drug is administered alone. In case therapeutic doses of anticoagulants are started during the Treatment Period, international normalized ratio and activated partial thromboplastin time (or partial thromboplastin time) will be repeated **3 days prior to each cycle**.
17. Urinalysis tests, including red blood cells, glucose, ketones, leukocytes, nitrites, pH, and proteins, will be performed at baseline, before each cycle and at the Safety Follow-up Visit. For all women of childbearing potential, a urine pregnancy test must be done before each cycle (when a serum test is not performed; see Footnote 10), then monthly until 6 months after the Safety Follow-up Visit. If a urine test is found to be positive, the pregnancy must be confirmed with a serum test (beta human chorionic gonadotropin) via the local laboratory.
18. PK blood samples will be collected from all patients at Cycle 1 **within 7 days** prior to infusion at the time of blood sampling for assessment of hematology, baseline level of shed antigen, and the test for antibodies against trastuzumab (ADA/NADA). Then, starting at Cycle 3, **within 3 days** prior to infusion every 3 cycles (approximately every 9 weeks; Cycles 6, 9, 12, and 15), PK samples will be collected at the same time as sample collections to assess for the presence of ADA/NADA while on treatment with

HLX02 or Herceptin®. Extended PK collections will be collected from all patients in Cycle 1 on Day 1 at the end of infusion, then at Cycles 4 and 8 prior to infusion (at the same time as blood sampling for assessment of hematology) and Cycle 8 Day 1 at the end of infusion.

19. Blood samples to test for antibodies against trastuzumab (ADA/NADA) must be collected in all patients **within 7 days prior** to the first administration of study drug and, starting at Cycle 3, **within 3 days** prior to study drug infusion every 3 cycles (approximately every 9 weeks; Cycles 6, 9, 12, and 15) subsequently, and also at the Safety Follow-up Visit. While on treatment, the samples should be collected at the same time as the PK sample (and blood sampling for hematology).

4.2 Discussion of Study Design

This study is designed to compare the efficacy, and to evaluate safety and immunogenicity of HLX02 and EU-sourced Herceptin® when administered in combination with docetaxel in patients with HER2-positive, recurrent or previously untreated metastatic breast cancer. The design is considered appropriate for the evaluation of biosimilarity of HLX02 to Herceptin® as it complies with EMA biosimilar guidelines.

A double-blind, randomized design is used to avoid bias in the assessment of the primary endpoint of tumor measurement and ensure that the outcome is not affected by known and unknown differences in prognostic factors between treatment arms. The standard chemotherapy chosen is docetaxel, based on the reference study conducted with the comparator.[6] Such a regimen is a widely-used standard combination, the efficacy of which was recently further documented in a large pivotal study where the combination was used as the control regimen.[10] Moreover, docetaxel allows a 3-weekly schedule that is less demanding than the weekly schedule recommended for paclitaxel.

The dose of HLX02 was selected as per the Herceptin® label for a 3-weekly regimen, i.e. Herceptin® as a loading dose of 8 mg/kg and maintenance dose of 6 mg/kg every 3 weeks. This regimen was shown to be well tolerated and beneficial in patients with HER2-overexpressing metastatic breast cancer. A treatment period of at least 8 cycles is considered adequate for the comparison of ORR since most patients will have achieved tumor shrinkage by that time. Patients showing benefit from treatment will continue for a maximum of 12 months of treatment, or until Investigator-assessed disease progression, excessive toxicity, Investigator's judgment, withdrawal of consent, lost to follow-up, death, start of a new anticancer therapy, or study termination by the Sponsor, whichever occurs first.

Endpoints of ORR and PFS based on tumor assessments using RECIST 1.1 are widely used and accepted measurements of efficacy in oncology studies; however, in accordance with EMA guidelines, for the purpose of demonstrating biosimilarity, the most sensitive endpoint must be chosen to allow the detection of differences between the 2 treatment arms. In metastatic breast cancer, the most sensitive endpoint is ORR, and since the study aims to compare ORR up to Week 24, ORR_{24} was chosen to establish biosimilarity. The calculation of equivalence margins is discussed in Section 8.1.

Blood samples to determine trastuzumab concentrations will be collected each time a blood sample is collected for ADA/NADA assessment while on treatment. This will allow determination as to whether potential ADA/NADA formation may affect trastuzumab exposure and the interpretation of efficacy and/or safety findings. A limited number of additional PK blood samples will be collected during the first 8 cycles of treatment to

measure the exposure to trastuzumab following HLX02 or Herceptin® and, if appropriate, to initiate additional PopPK analyses and/or correlate trastuzumab exposure and response (safety, immunogenicity and/or efficacy). Baseline level of shed antigen level will be collected.

4.3 Selection of Study Population

4.3.1 Inclusion Criteria

Patients may be entered in the study only if they meet all of the following criteria:

1. Patients have voluntarily agreed to participate and given written informed consent.
2. Male or female ≥18 years of age on day of signing the informed consent form (ICF).
3. Histologically or cytologically confirmed adenocarcinoma of the breast.
4. Recurrent disease not amenable to curative surgery or radiation therapy, or metastatic disease with an indication for a taxane-containing therapy.
5. Availability of formalin-fixed paraffin-embedded (FFPE) tissue block from the primary tumor, or a metastatic lesion, to confirm HER2-positivity by the central laboratory, based on FISH amplification ratio ≥2.0 or IHC score 3+, and for hormone status (ER/PgR) determination (local or central laboratory).[11] If not possible, a fresh biopsy is required (see Section 6.4.2).
6. No prior systemic anticancer agent such as chemotherapy, biological or targeted agent for metastatic disease with the exception of hormonal therapy, which must be stopped at least 2 weeks before randomization. Use of herbal remedies or traditional Chinese medicines for anticancer, hematologic or liver function, or anti-infective treatment must be stopped at the time of the ICF signature (at least 2 weeks before randomization).
7. For patients with recurrent disease, prior neo-/adjuvant therapy containing trastuzumab and/or lapatinib must have been stopped at least 12 months before the diagnosis of recurrent (local or metastatic) disease (i.e. a disease-free interval of ≥12 months). If trastuzumab/lapatinib was not used, prior neo-/adjuvant therapy with a taxane must have been stopped at least 6 months before the diagnosis of recurrent (local or metastatic) disease (i.e. a disease-free interval of ≥6 months). If only other cytotoxics were given, they must be stopped at least 4 weeks before randomization. Any hormonal therapy must be stopped at the time of the ICF signature (at least 2 weeks before randomization).
8. Measurable disease (at least one measurable target lesion assessed by CIR; bone-only or central nervous system [CNS]-only metastases are not allowed).

9. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

10. LVEF within institutional range of normal at baseline (within 42 days before randomization) as determined by either echocardiography (ECHO) or multigated acquisition (MUGA) scan.

11. Adequate hematologic, hepatic and renal function as indicated by the following laboratory values:

    - Absolute neutrophil count (ANC) ≥1,500/mL without granulocyte-colony stimulating factor (G-CSF) or other medical support
    - Platelets ≥100,000/mL
    - Hemoglobin ≥9 g/dL without transfusion or other medical support within 14 days
    - Serum creatinine ≤1.5 x upper limit of normal (ULN) and creatinine clearance rate ≥50 mL/min, calculated according to Cockroft-Gault formula (Note: if the calculated creatinine clearance is <50 mL/min, a 24-hour creatinine clearance test may be requested by the Investigator for confirmation. Patients with a 24-hour creatinine clearance <50 mL/min should be excluded)
    - Serum total bilirubin ≤1.5 x ULN (unless the patient has documented Gilbert's syndrome) without any medical support within 14 days
    - Serum aspartate aminotransferase/glutamic-oxaloacetic transaminase (AST/SGOT) or serum alanine aminotransferase/glutamate-pyruvate transaminase (ALT/SGPT) ≤2.5 x ULN (≤5 x ULN in the case of liver metastases) provided alkaline phosphatase (ALK) is ≤2.5 x ULN. In the case of bone metastasis, serum ALK can be >2.5 x ULN if AST and ALT are ≤1.5 x ULN without any medical support within 14 days
    - International normalized ratio (INR), and activated partial prothrombin time (aPTT) or partial prothrombin time (PTT) ≤1.5 x ULN.

12. Estimated life expectancy ≥3 months.

13. Female patients are eligible to enter and participate in the study if they are of:

    - Non-childbearing potential (i.e. physiologically incapable of becoming pregnant), including any female who:
        - Has had a hysterectomy
        - Has had a bilateral oophorectomy (ovariectomy)
        - Has had a bilateral tubal ligation
        - Is postmenopausal (total cessation of menses for ≥1 year)

- Childbearing potential, have a negative serum pregnancy test at Screening (within 7 days of the first investigational/comparator product administration), are not breast feeding, and use highly-effective or acceptable contraceptive measures (no oral, injected or implanted hormonal methods are allowed) before study entry and throughout the study until 7 months after the last investigational/comparator product administration. Highly-effective or acceptable contraceptive measures, when used consistently and in accordance with both the product label and the instructions of the physician, are defined as follows:
  - Vasectomized partner who is sterile prior to the female patient's entry and is the sole sexual partner for that female
  - Any intrauterine device with a documented failure rate of less than 1% per year
  - Double-barrier contraception (considered acceptable but not highly effective), defined as condom with spermicidal jelly, foam, suppository, or film; OR diaphragm with spermicide; OR male condom and diaphragm
  - Male partners must agree to use a highly-effective non-hormonal form of contraception or 2 effective forms of non-hormonal contraception. Contraception use must continue for the duration of study treatment and for at least 7 months after the last dose of study treatment.

14. Male patients with partners of childbearing potential are eligible to enter and participate in the study if they, and their female partners, are willing to use highly-effective or acceptable contraceptive measures before study entry and throughout the study until 7 months after the last investigational/comparator product administration. Highly-effective or acceptable contraceptive measures, when used consistently and in accordance with both the product label and the instructions of the physician, are defined as follows:

    - No oral, injected or implanted hormonal contraceptive methods are allowed for male patients but can be used by their female partners
    - Vasectomized male patient who is sterile prior to the patient's entry and has one sexual partner
    - Any intrauterine device with a documented failure rate of less than 1% per year
    - Double-barrier contraception (considered acceptable but not highly effective), defined as condom with spermicidal jelly, foam, suppository, or film; OR diaphragm with spermicide; OR male condom and diaphragm.

4.3.2 Exclusion Criteria

Patients will not be entered in the study for any of the following reasons:

1. Previously- or currently-treated (systemic chemotherapy, biological, or targeted agent, or any other anticancer agent) metastatic breast cancer with the exception of hormonal therapy.

2. Known brain metastasis or other CNS metastasis that is either symptomatic or untreated. Central nervous system metastases that have been treated by complete resection and/or radiotherapy demonstrating stability or improvement are not an exclusion criterion provided they are stable as shown by computed tomography (CT) scan for at least 4 weeks before Screening without evidence of cerebral edema and no requirements for corticosteroids or anticonvulsants.

3. Participation in another clinical study within 4 weeks before enrollment (3 months for studies involving monoclonal therapy) or the intention of participating in another clinical study during any part of the study period.

4. History of other malignancy within the last 5 years, except for carcinoma in-situ of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin that has been previously treated with curative intent.

5. Known history of human immunodeficiency virus (HIV).

6. Clinically significant active infection requiring therapy; positive tests for hepatitis B (defined as the presence of hepatitis core antibody [HBcAb] or hepatitis B surface antigen [HBsAg], and hepatitis B virus-deoxyribonucleic acid [HBV-DNA] >1000 cps/mL or > lower limit of quantification according to the local laboratory method); or hepatitis C (hepatitis C antibody and/or hepatitis C virus ribonucleic acid [RNA]).

7. Underlying medical conditions or current severe, uncontrolled systemic disease that, in the Investigator's opinion, will make the administration of study drug hazardous. A major surgical procedure (defined as a procedure that would require more than 3 weeks without study treatment) within 4 weeks prior to enrollment or anticipation of the need for major surgery during the course of study.

8. Current uncontrolled hypertension (systolic >150 mmHg and/or diastolic >100 mmHg) or unstable angina.

9. History of chronic heart failure based on any New York Heart Association (NYHA) criteria, or left ventricular hypertrophy. Current serious cardiac arrhythmia requiring

treatment (except atrial fibrillation, paroxysmal supraventricular tachycardia) or clinically significant conduction defects as seen on electrocardiogram (ECG). History of myocardial infarction within 6 months of randomization. History of LVEF decline to below 50% during or after previous trastuzumab neo-adjuvant or adjuvant therapy. Significant cardiac murmurs either on examination or ECHO.

10. History of prior exposure to doxorubicin >360 mg/m² (or equivalent).

    Note: Equivalents include epirubicin >720 mg/m^2; mitoxantrone >120 mg/m^2; idarubicin >90 mg/m^2; liposomal doxorubicin or other anthracycline greater than the equivalent of 360 mg/m^2 of doxorubicin. If more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin.

11. Use of oral, injected or implanted hormonal methods of contraception.

12. Chronic daily use of corticoids (equivalent to >10 mg/day methylprednisolone) by oral intake (inhalation is permitted).

13. Known hypersensitivity to any of the study drugs.

14. Residual non-hematologic toxicity ≥ Grade 2 from prior therapy.

4.3.3 Patient Withdrawal

All patients are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrollment are to be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be withdrawn from the study and the Sponsor or the contract research organization, Quintiles, must be contacted.

Investigators may withdraw patients from the study and/or from study treatment in the event of intercurrent illness, AEs, protocol violation, administrative reasons, or for other reasons. Patients who prematurely withdraw from study treatment will continue being followed for post-treatment assessments at the Safety Follow-up Visit, unless patients withdraw consent. Excessive patient withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

If a patient decides to withdraw, all efforts should be made to complete and report study assessments as thoroughly as possible. The Investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing

from the study. If the reason for removal of a patient from the study is an AE, the principal specific event will be recorded on the eCRF.

5.0 STUDY TREATMENTS

5.1 Treatments Administered

Patients will be randomized to 1 of 2 treatment arms:

Arm A, HLX02 (investigational product) + docetaxel

- HLX02 8 mg/kg administered intravenously over 90 minutes as a loading dose on Day 1, Cycle 1 then 6 mg/kg every 3 weeks for subsequent cycles.

Or

Arm B, EU-sourced Herceptin® (comparator) + docetaxel

- EU-sourced Herceptin® 8 mg/kg administered intravenously over 90 minutes as a loading dose on Day 1, Cycle 1 then 6 mg/kg every 3 weeks for subsequent cycles.

In both treatment arms, treatment with HLX02 or Herceptin® will continue for a maximum of 12 months (17 cycles), or until Investigator-assessed disease progression, excessive toxicity, Investigator's judgment, withdrawal of consent, lost to follow-up, death, start of a new anticancer therapy, or study termination by the Sponsor, whichever occurs first.

In both treatment arms docetaxel 75 mg/m^2 will be administered on Day 2, Cycle 1. All patients will be given prophylactic dexamethasone (see Section 5.8.2). If well tolerated, as determined by the Investigator, then the same dose will be given every 3 weeks on **Day 1 of each subsequent cycle <u>always after</u> HLX02 or Herceptin®**. Each dose will be administered intravenously over 60 minutes according to the currently approved prescribing information. Treatment with docetaxel will continue for at least 8 cycles unless there is disease progression or excessive toxicity. After Cycle 8, continuation of docetaxel treatment is at the discretion of the Investigator. Once Herceptin®/HLX02 is no longer being given in combination with docetaxel and the patient has tolerated a number of Herceptin®/HLX02 infusions, dexamethasone need not be given; however, this will depend on each individual case, local standard practice, and the Investigator's judgment.

5.2 Identity of Investigational, Comparator, and Associated Products

<u>HLX02</u> (trastuzumab), the investigational product, is a recombinant anti-HER2 humanized monoclonal antibody for injection and is manufactured by Shanghai Henlius Biopharmaceuticals Co., Ltd (a wholly-owned subsidiary of Shanghai Henlius Biotech, Inc.).

The clinical preparation of HLX02 is a sterile, white to pale yellow, preservative-free, lyophilized powder. Each vial contains 150 mg of concentrated powder for solution for infusion. After reconstitution with sterile water for injection, the solution is a colorless or pale yellow, transparent liquid.

Herceptin® (trastuzumab), the comparator product, is a humanized immunoglobulin G1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture. The drug is manufactured by Roche Pharmaceuticals. The clinical preparation of Herceptin® is a white to pale yellow lyophilized powder. Each vial contains 150 mg of concentrated powder for solution for infusion. After reconstitution with sterile water for injection, the solution is a colorless or pale yellow, transparent liquid.[9]

Vials of HLX02 and Herceptin® should be stored in the refrigerator at 2 to 8ºC (36-46ºF). The reconstituted solution is physically and chemically stable for 48 hours at 2 to 8°C. Solutions for intravenous infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/mL (0.9%) solution for injection for 24 hours at temperatures not exceeding 30°C (86°F).

Study drug will be supplied to the centers by a third party vendor.

Docetaxel, the associated product, will be supplied centrally. Refer to the docetaxel currently approved prescribing information on formulation, preparation, storage, and administration.

5.3 Packaging and Labelling

Vials of HLX02 and EU-Herceptin® will be labelled by a third party. The labels will contain the following information: the pharmaceutical dosage form, route of administration, identification number, the protocol number, use-by date, storage details, and all other details required by local regulations and Good Manufacturing Practice.

5.4 Method of Assigning Patients to Treatment Arm

Once the patient meets all eligibility criteria, the study center will request the study medication assignment using the Interactive Web Response System/Interactive Voice Response System (IWRS/IVRS).

All randomized patients will be managed by IWRS/IVRS. Designated study personnel at the investigational centers will be assigned password-protected, coded identification numbers, which give them authorization to access the IWRS/IVRS to randomize patients. The system will present a menu of questions by which the study personnel will identify the patient and confirm eligibility. When all questions have been answered, the IWRS/IVRS will assign a

randomization identification number. Confirmation of the randomization will be sent via fax to the investigational center, the Sponsor and Quintiles representatives.

A complete block randomization scheme will be applied to achieve balance in treatment assignment within each of the strata, as defined by the following stratification factors: ER/PgR status, prior neo-/adjuvant therapy with Herceptin®, and ethnicity (Asian and non-Asian).

5.5 Selection of Doses in the Study

The dose of HLX02 was selected as per Herceptin® label for a 3-weekly regimen. In these studies, Herceptin® as a loading dose of 8 mg/kg and maintenance dose of 6 mg/kg every 3 weeks was well tolerated and beneficial in patients with HER2-overexpressing metastatic breast cancer.[9]

A starting dose of docetaxel 75 mg/m^2 is in accordance with the currently approved prescribing information.

5.6 Selection and Timing of Dose for Each Patient

5.6.1 Administration

On Day 1 of every treatment cycle, body weight will be used to calculate the required dose of HLX02 or Herceptin® and docetaxel (study drug). All patients will be given prophylactic dexamethasone (see Section 5.8.2). The Investigator must make sure that any weight change is not due to fluid retention. If it is due to fluid retention, the patient must be given oral furosemide (or equivalent diuretic). The dose will be adjusted only if the patient's weight changes by more than ±10% from baseline. Any change in dose must be documented in the eCRF.

If either HLX02/Herceptin® or docetaxel must be delayed for a day or more (maximum 14 days), both agents should be delayed for the same timeframe. If delayed by more than 14 days, the agent that led to the delay will be omitted and given at the next scheduled cycle.

Administered dose of all study drugs, date/time of start of infusion, date/time of end of infusion and any interruptions must be documented in the eCRF. Interruptions should be documented as time the infusion stopped and time that the infusion is restarted.

HLX02 or Herceptin®

On Day 1, Cycle 1, either HLX02 or Herceptin® will be administered as an intravenous loading dose of 8 mg/kg over 90 minutes, then 6 mg/kg on Day 1 of every subsequent cycle (i.e. every 3 weeks) over 30-90 minutes (i.e. any duration between 30 and 90 minutes from Cycle 2 onwards) if the previous dose was well tolerated.

Appropriate aseptic technique should be used. Each vial of the study drug is reconstituted with 7.2 mL of water for injection. Use of other reconstitution solvents should be avoided. This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab. A volume overage of 4% ensures that the labelled dose of 150 mg can be withdrawn from each vial.

The drug should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted drug may result in problems with the amount of solution that can be withdrawn from the vial:

- Using a sterile syringe, slowly inject 7.2 mL of water for injection in the vial containing the study drug, directing the stream into the lyophilized cake.
- Swirl vial gently to aid reconstitution. DO NOT SHAKE.

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted drug should be essentially free of visible particulates.

Volume of the solution required:

$$\textbf{Volume}\ (in\ mL) = \frac{\textbf{Body Weight}\ (in\ kg) \times \textbf{Dose}\ (8\ mg/kg\ for\ loading\ or\ 6\ mg/kg\ for\ maintenance)}{\textbf{21 mg/mL}\ (concentration\ of\ reconstituted\ solution)}$$

The appropriate amount of solution should be withdrawn from the vial and added to a polyvinylchloride, polyethylene or polypropylene infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with glucose-containing solutions. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately over 90 minutes for the loading dose or 30-90 minutes for the maintenance dose. The study drug should always be administered **before docetaxel**.

Docetaxel

On Day 2, Cycle 1, docetaxel 75 mg/m^2 will be administered over 60 minutes according to currently approved prescribing information. If well tolerated, as determined by the Investigator, then the same dose will be given every 3 weeks on Day 1 of each subsequent cycle **always starting 60 minutes after the end of the HLX02 or Herceptin® infusion**. As of Cycle 2, according to tolerance and local practice, the Investigator can increase the dose of docetaxel to 100 mg/m² (see Section 5.6.3).

5.6.2 HLX02 and Herceptin® Main Toxicities and Administration Modifications

In case the whole loading dose of HLX02 or Herceptin® could not be administered due to an infusion reaction or other reason, the following guidelines apply:

- The patient should receive at least 50% of the loading dose in the first week. Therefore, if the patient receives less than 50% of the Cycle 1 dose, the patient should receive the remainder before Day 22, preferably within the first week. Thereafter, the patient should receive the usual maintenance dose 3 weeks after the first interrupted dose, as routinely scheduled. For example, if a patient received only approximately 50% of the scheduled loading dose (i.e. only 4 mg/kg instead of 8 mg/kg), the patient should receive the remaining dose (4 mg/kg), preferably in the first week, and then regular maintenance doses (6 mg/kg) on Day 22, as routinely scheduled.
- If the patient receives between 50–75% of the dose, the patient should receive the remainder before Day 22, preferably within the first 2 weeks of Cycle 1. For example, if a patient received only approximately 60% of the scheduled loading dose, the patient should receive the remaining 40%, within 2 weeks after the interrupted loading dose. Thereafter, the patient should receive the regular maintenance doses on Day 22, as routinely scheduled.
- If the patient receives ≥75% of the loading dose, additional loading is probably not necessary. However, the remainder of the loading dose may be given at the Investigator's discretion. In such a case, the remainder may be given at any time before the next scheduled dose or the patient may be given an additional loading dose on Day 22. If, after receiving an incomplete loading dose on Day 1, the patient cannot attend the site until Day 22, the patient should receive a second loading dose on Day 22. However, every effort should be made to give the remainder of the dose prior to Day 22.

In the case of toxicity, HLX02 and Herceptin® administration may be delayed but no dose reduction is allowed. If a patient misses a dose of HLX02 or Herceptin® by less than 1 week after the planned date, the usual maintenance dose (6 mg/kg) should be given as soon as possible. Do not wait until the next planned cycle. If a patient misses a dose of HLX02 or Herceptin® for ≥1 week (i.e. the 2 sequential administrations are given ≥4 weeks apart), a re-loading dose of HLX02 or Herceptin® (8 mg/kg) should be given. Subsequent maintenance HLX02 or Herceptin® doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later. If re-loading is required, docetaxel administration (at the dose that was last tolerated) will be restarted on the same day as the re-loading dose, to coincide with the start of a new cycle. If a patient has a study drug interruption ≥9 weeks for a trastuzumab-related toxicity, they will be discontinued from the study (see the Herceptin® package insert for further details).

In general, AEs that occur in patients enrolled in this study can be managed referring to the Herceptin® package insert or following standard practice at the study site. Guidance for managing specific reactions (cardiac dysfunction; IRRs and hypersensitivity; hematologic toxicity; pulmonary events) is provided below.

Cardiac Dysfunction

At baseline all patients must have LVEF within institutional range of normal and LVEF will be monitored in accordance with the Schedule of Events (see Table 4-1). If an Investigator is concerned that an AE may be related to cardiac dysfunction, an additional LVEF measurement should be performed (see Section 6.2.1.3 for details on reporting cardiac AEs).

The safety of continuation or resumption of trastuzumab in patients who experience cardiac dysfunction has not been prospectively studied. Either reference trastuzumab or HLX02 must be withheld for at least 4 weeks if ≥16% absolute decrease in LVEF from pre-treatment levels or LVEF is below institutional normal range and ≥10% absolute decrease in LVEF. A repeat LVEF assessment must be performed within approximately 3 weeks. Treatment resumption is allowed if within 4-8 weeks the LVEF returns to within normal limits and the absolute decrease from baseline is ≤15%. Treatment should be discontinued for a persistent (>8 weeks) decline in LVEF or on suspension of treatment on more than three occasions for cardiac toxicity.[12] All such patients should be referred for assessment by a cardiologist and followed up. If symptomatic cardiac failure develops during study treatment, it should be treated with standard medicinal products for CHF.[9] Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal studies improved with standard CHF treatment consisting of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin® treatment continued on therapy without additional clinical cardiac events.

Trastuzumab may persist in the circulation for up to 7 months after stopping the treatment based on population PK analysis of all available data.[9] Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Infusion-related Reactions and Hypersensitivity

Serious IRRs to the study drug infusion including dyspnea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported.[9] The majority of these events occur during or within 2.5 hours of the start of the first infusion. If

an IRR occurs, the infusion should be immediately interrupted (in patients with non-serious IRRs, at the Investigator's discretion, the infusion may be slowed) and the patient should be monitored until resolution of all observed symptoms.

These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. If a second episode of serious IRR occurs despite prophylactic use of steroids (see Section 5.8.2) treatment will be permanently discontinued.

In rare cases, these serious reactions are associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction; therefore, these patients should not be treated with trastuzumab.

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to 1 week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than 6 hours after the start of the trastuzumab infusion.

Hematologic Toxicity

Febrile neutropenia and leukopenia have occurred very commonly after infusion with trastuzumab.[9] Commonly occurring adverse reactions include anemia, thrombocytopenia and neutropenia. The frequency of occurrence of hypoprothrombinemia is not known. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Pulmonary Events

Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting.[9] These events have occasionally been fatal. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. These events may occur as part of an IRR or with a delayed onset. Patients experiencing dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with trastuzumab.

Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

5.6.3 Docetaxel Dose Modifications

Any docetaxel dose increase or decrease should be documented in the eCRF (see Section 5.6.1). All patients will be given prophylactic dexamethasone (see Section 5.8.2 for regimen). If an IRR occurs, the infusion should be immediately interrupted (in patients with non-serious IRRs, at the Investigator's discretion, the infusion may be slowed) and the patient should be monitored until resolution of all observed symptoms.

Dose Increase

After an initial dose of docetaxel, patients who do not experience febrile neutropenia, severe or cumulative cutaneous reactions, or severe peripheral neuropathy may tolerate higher doses. Consequently, at the Investigator's discretion, the dose of docetaxel can be increased to 100 mg/m^2 in patients who have tolerated at least 1 administration of 75 mg/m^2 without any of the following:

- Febrile neutropenia (≥38.5ºC and neutrophils <500 cells/mm^3 for more than 1 week)
- Grade 4 neutropenia for more than 5 days
- ANC <100/μL for more than 1 day; or
- Any non-hematological toxicities of > Grade 2 (National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 [NCI-CTCAE v4.03]).

If treatment is withheld for more than 1 week for granulocyte recovery, or if a febrile neutropenic episode (≥38.5ºC and neutrophils <500 cells/mm^3 for more than 1 week) occurs at any time during therapy, prophylactic G-CSF will be administered (according to the package insert) with all subsequent cycles. Prophylactic use of G-CSF **before the first cycle** is not allowed unless the patient had prior severe neutropenia during neo-/adjuvant therapy.

The recommendations given in the prescribing information for docetaxel should be strictly followed.

Dose Delay

Docetaxel may be delayed due to toxicities. If docetaxel is delayed for more than 3 weeks with no recovery, the patient should be withdrawn from docetaxel treatment.

Dose Decrease

Docetaxel dose modifications will be allowed for myelosuppression, hepatic dysfunction, and other toxicities according to the parameters in Table 5-1.

Table 5-1 Docetaxel Dose Adjustments

Docetaxel Dose	When
75 mg/m^2	Starting dose: • Administer only if neutrophil count is ≥1500 cell/mm^3
55 mg/m^2 (or 75 mg/m^2 if dose previously increased to 100 mg/m^2)	25% reduced dose in case of any of the following toxicities: • Febrile neutropenia or neutrophils <500 cells/mm^3 for more than 1 week (after fully recovering to a neutrophil count ≥1,500 cells/mm^3) • Platelet count <100,000 cells/mm^3 (after recovering to a platelet count ≥100,000 cells/mm^3) • Severe or cumulative cutaneous reactions
Permanently discontinue docetaxel	After any of the following toxicities: • Severe hypersensitivity reactions • Peripheral neuropathy ≥ Grade 3 (without recovery after delay of 3 weeks) • Severe or cumulative cutaneous reactions that continue at a dose of 55 mg/m^2 without recovery • Febrile neutropenia or neutrophils <500 cells/mm^3 without recovery • Platelet count <100,000 cells/mm^3 without recovery • Serum total bilirubin >1.5 x ULN without recovery • Serum transaminase (AST/ALT) levels >1.5 x ULN concurrent with serum ALK levels >2.5 x ULN (unless there is bone metastasis)

ALK = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

At any time during the Treatment Period, docetaxel should be discontinued for progressive disease or unacceptable toxicity. If, despite adequate prophylaxis with dexamethasone (or equivalent), a severe IRR occurs, docetaxel will be permanently discontinued. After Cycle 8, continuation of docetaxel treatment is at the discretion of the Investigator.

If docetaxel is permanently discontinued for any reason other than disease progression, the patient can continue on HLX02 or Herceptin® alone if they are still benefiting from the treatment.

5.7 Blinding

This is a randomized, double-blind, bioequivalence study with limited access to the randomization code. The treatment each patient receives will not be disclosed to the Investigator, study center staff, patient, Sponsor, or Quintiles with the exception of the

designated unblinded study team at the time of the first database lock for the primary analysis.

The vials of HLX02 and Herceptin® are not identical in appearance. To ensure the Investigator and patient stay blinded, an unblinded pharmacist team at each center will reconstitute the study drug for each patient. After the drug has been reconstituted, the unblinded pharmacist or designee will label the intravenous bag with the correct patient number so the study team will not know what treatment is contained therein.

The blind must not be broken during the course of the study **unless**, in the opinion of the Investigator, it is absolutely necessary to safely treat the patient. If it is medically imperative to know what study drug the patient is receiving, the study drug should be temporarily discontinued if, in the opinion of the Investigator, continuing the drug could negatively affect the outcome of the patient's treatment.

The decision to break the blind in emergency situations remains the responsibility of the Investigator and will not be delayed or refused by the Sponsor; however, the Investigator may contact the Quintiles Medical Monitor prior to breaking the blind to discuss the unblinding and what would be in the best interests of the patient. The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Quintiles Medical Monitor of the emergency unblinding and the reason for breaking the blind and this should be clearly documented by the Investigator in the patient's source documentation. The process for breaking the blind will be handled through the IWRS/IVRS using an emergency unblinding personal identification number. If the blind is broken, it may be broken for only the patient in question.

5.8 Prior and Concomitant Treatments

At Screening, all medications taken in the 90 days before randomization, including anticancer therapies, will be recorded on the eCRF. Prior anticancer treatments, including but not limited to neo-/adjuvant therapy and hormone therapy, should also be recorded on the eCRF at Screening.

All concomitant medications including herbal remedies and traditional Chinese medicines must be recorded on the eCRF.

5.8.1 Excluded Medications

The use of excluded medication is a protocol violation and should be recorded in the eCRF. The following is not permitted during the study:

- Treatment with other systemic anticancer agents (e.g. chemotherapy, hormonal therapy, immunotherapy). To lessen the risk of resistance, prior neo-/adjuvant therapy containing trastuzumab and/or lapatinib must have been stopped at least 12 months before the diagnosis of recurrent (local or metastatic) disease (a disease-free interval of ≥12 months). If trastuzumab/lapatinib was not used, prior neo-/adjuvant therapy with a taxane must have been stopped at least 6 months before the diagnosis of recurrent (local or metastatic) disease (a disease-free interval of ≥6 months). Use with other cytotoxics must have been stopped at least 4 weeks before randomization. Any hormonal therapy must be stopped at the time of the ICF signature (at least 2 weeks before randomization).
- Use of oral, injected or implanted hormonal methods of contraception.
- Concurrent investigational agents of any type.
- Chronic daily use of corticoids (equivalent to >10 mg/day methylprednisolone) by oral intake (inhalation is permitted). Such use must be stopped at least 28 days before first infusion with no planned requirement for the corticoid over the next 12 months.
- Herbal remedies and traditional Chinese medicines for anticancer, hematologic or liver function, or anti-infective treatment are prohibited during the study. Herbal remedies and traditional Chinese medicines must be stopped at the time of the ICF signature (at least 2 weeks before randomization).
- No other therapeutic modality is permitted such as intrathecal therapy or radiotherapy.

5.8.2 Allowed Medications

Prophylactic steroids

To decrease the risk of IRRs and nausea/vomiting, all patients treated with docetaxel will be given either oral or intravenous dexamethasone as follows:

Oral: on Day 2 of Cycle 1, patients will be given 7.5-8 mg (depending on the available tablet dosage form) dexamethasone orally at 24 hours (about the same time as the HLX02 or Herceptin® infusion on Day 1) and 12 hours before the start of the docetaxel infusion. In subsequent cycles (Cycle 2 onwards), administration of 7.5-8 mg dexamethasone orally will occur at 24 hours and 12 hours before the HLX02 or Herceptin® infusion, followed 1 hour

later by the docetaxel infusion. After the docetaxel infusion, 7.5-8 mg dexamethasone should be given twice daily for a further 48 hours.

Intravenous: on Day 2 of Cycle 1, patients will be given 20 mg dexamethasone intravenously approximately 30 minutes before the start of the docetaxel infusion. In subsequent cycles (Cycle 2 onwards), patients will be given 20 mg dexamethasone intravenously after the HLX02 or Herceptin® infusion and before the docetaxel infusion. After the docetaxel infusion, 7.5-8 mg dexamethasone should be given twice daily for 48 hours as described above.

Once Herceptin®/HLX02 is no longer being given in combination with docetaxel, and the patient has tolerated a number of Herceptin®/HLX02 infusions, dexamethasone need not be given; however, this will depend on each individual case, local standard practice, and the Investigator's judgment.

Other allowed medications

Patients should receive full supportive care including transfusion of blood and blood products, antibiotics, etc., according to standard of care when necessary.

All protocol-allowed medications taken by the patient for concomitant disease should continue as necessary during the study. Treatments prescribed to patients should be adapted according to the local standard of care practice. The following list of allowed medications is provided as guidance:

• Anti-emetics:	If required
• Anti-coagulation therapy:	Permitted for maintenance of patency of permanent indwelling intravenous catheters
• Paracetamol (acetaminophen) or other analgesics:	If required
• Anti-diarrhea medication:	If required, e.g. loperamide
• Granulocyte-colony stimulating factor:	May be used according to the product license and according to the currently approved prescribing information for docetaxel and American Society of Clinical Oncology clinical guidelines.[13] Granulocyte-colony stimulating factor may not be given as prophylaxis before the first cycle (see Section 5.6.3).

- Bisphosphonates: Administered according to their label instructions at the discretion of the Investigator according to local practice.

5.9 Medical Care of Patients after the End of the Treatment Period

At the defined end of the Treatment Period (up to 12 months), patients will be referred to the local institution and will continue therapy in accordance with local practice. The Sponsor will not provide any additional care to patients after they leave the study because such care should not differ from what is normally expected for patients with breast cancer.

5.10 Treatment Compliance

The prescribed dosage of HLX02 or Herceptin® and the route of administration may not be changed and administration may only be delayed in the case of toxicity (see Section 5.6). Any deviations from the intended regimen must be recorded in the source documents and eCRFs.

5.11 Study Medication Accountability

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study drugs using the Drug Accountability Form. These forms must be available for inspection at any time.

All study medication supplies should be accounted for at the termination of the study and a written explanation provided for discrepancies. All unused study drug supplies and packaging materials are to be inventoried and returned to the Sponsor or designee by the Investigator. The Investigator is not permitted to return or destroy unused clinical drug supplies or packaging materials unless authorized by the Sponsor or designee.

6.0 EFFICACY, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

6.1 Efficacy

6.1.1 Primary Efficacy

Primary efficacy assessment (ORR_{24}) will be conducted by CIR for an independent, blinded determination of tumor response up to Week 24 after completion of up to 8 cycles of treatment.

6.1.1.1 Tumor Assessments

The tumor measurement at Screening will be reviewed by CIR to confirm eligibility before the patient can be randomized. For further details on who will conduct the tumor assessments during the study, see Section 6.1.1.2. Assessments to evaluate tumor response during the study will be performed according to the Schedule of Events (Table 4-1). Assessments will be based on enhanced CT or magnetic resonance imaging (MRI) scan results; the tumor size will be measured and the overall response will be assessed according to RECIST 1.1. A summary of RECIST 1.1 is provided in Appendix 4. Tumor assessments will be recorded on the eCRF.

The same tumor assessment technique must be used throughout the study for response evaluation. Positron emission tomography (known as PET scan) is not accepted as a sole method to assess efficacy. Enhanced CT/MRI is preferred and if used, must be used throughout the study period. The minimum CT or MRI scans at Screening (baseline) examination should include:

- CT or MRI scan of the chest and abdomen (including liver, spleen, and adrenals), and pelvis if clinically indicated
- CT or MRI scan of the brain and/or spine where there is clinical suspicion of CNS metastases
- An isotope bone scan (with bone X-ray[s] as necessary) at baseline if clinically indicated. It should be repeated during the study in the event of clinical suspicion of progression of existing bone lesions and/or the appearance of new bone lesions
- Medical photography to monitor (sub) cutaneous skin lesions.

For patients with multiple measurable lesions, a maximum of 2 lesions per organ and 5 lesions in total that are representative of all involved organs should be designated as target lesions and recorded and measured at Screening.

All other lesions should be identified as non-target lesions and should be recorded at baseline. Measurements of these lesions are not required but the presence or absence of each should be noted throughout the Treatment Period.

In cases where there is suspicion of progression before the next scheduled assessment, an unscheduled assessment is to be performed. The reason for the unscheduled assessment will be reported on the eCRF.

Tumor assessments will be performed at Week 6, 12, 18, and 24, regardless of the number of cycles actually given, and then every 9 weeks (between Days 15-21 after Cycles 11, 14, and 17); see the Schedule of Events (Table 4-1). If a tumor assessment must be performed early or late, subsequent assessments will be performed at the planned date **if at least 4 weeks apart**. Every effort should be made to maintain the planned schedule for tumor assessments every 6 weeks up to Week 24 and every 9 weeks up to 12 months.

For patients who discontinue study drug for reasons other than death, Investigator-assessed disease progression, excessive toxicity, or withdrawal of consent, efforts should be made to continue to perform scheduled tumor assessments for up to a maximum of 12 months, or until patient death, Investigator-assessed disease progression, withdrawal of consent, or start of a new anticancer therapy.

6.1.1.2 Central Independent Review of MRI/CT Scans and Local Imaging Assessment

All imaging and overall response assessments will be made according to RECIST 1.1 (see Appendix 4). Tumor measurements will be assessed by CIR at Screening (baseline) to determine eligibility before randomization can occur. During the Treatment Period, all treatment decisions will be made by the Investigator using tumor assessments by the local radiologist. Imaging performed at Week 6, 12, 18, and 24 will be sent for CIR to compare the pattern of response. Best ORR up to Week 24 by CIR will be used for the primary efficacy analysis. After Week 24, the response evaluation will be made by the local Investigator/radiologist and no CIR will be performed. Response duration will be evaluated by the local Investigator/radiologist if progression is documented after Week 24 imaging.

Images for the CIR must be acquired according to Imaging Guidelines provided by the vendor and then transmitted to the CIR facility. In addition, bone scans, x-rays, cytologic data (e.g. relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.), baseline scans, and relevant clinical information including medical photography will be forwarded to the CIR facility to aid in the overall response assessment.

Full details are listed in the CIR Charter and in the Imaging Guidelines.

6.1.2 Efficacy Endpoints

The primary endpoint is the ORR_{24}, calculated as the proportion of patients with a best response of CR or PR from first assessment up to Week 24 according to RECIST 1.1. The response does not need to be confirmed. Overall tumor response will be assessed by blinded, independent CIR according to RECIST 1.1.

The secondary endpoints are the following:

- ORR at Week 6, 12, 18, and 24 by CIR
- DoR, defined as the time form first documentation of CR or PR to the first documentation of progression up to 12 months after randomization. After Week 24, assessments are made by the Investigator
- DCR, defined as the proportion of patients who achieve CR, PR, or SD of at least 12 weeks
- CBR, defined as the proportion of patients who achieve CR, PR, or durable SD (SD ≥24 weeks)
- PFS up to 12 months, defined as the probability of being alive without documented progression 12 months after randomization, calculated using the Kaplan-Meier method
- OS at 12, 24, and 36 months, defined as the probability of being alive 12, 24, and 36 months after randomization, calculated using the Kaplan-Meier method.

Progressive disease is defined as at least a 20% increase in the sum of the diameters of target lesion(s), taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)

Patients will undergo Survival Follow-up every 3 months during the 12-month Treatment Period; thereafter, survival data will be collected every 3 months by telephone call up to 36 months after randomization.

Stable disease is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

6.2 Safety

6.2.1 Adverse Events

Definition of AE: An AE is any untoward medical occurrence in a patient 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 (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Definition of serious adverse event (SAE): An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death
- Is life-threatening (the patient is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Other: Medically significant events, which do not meet any of the criteria above, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g. neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.

Events that do not meet the definition of a SAE

Elective hospitalizations to administer, or to simplify study treatment or study procedures (e.g. an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g. undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events not to be considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as baseline medical conditions, and are NOT to be considered as AEs/SAEs. Progression of disease is not to be reported as an AE/SAE (see Section 6.2.1.7). With regard to laboratory values, see under 'Abnormal laboratory findings and other abnormal investigational findings' below.

Adverse events of special interest (AESI)

Certain AEs will be considered of special interest. These include, but may not be limited to, cardiac events (in particular CHF), infusion reactions, allergic-like reactions and hypersensitivity, and hematotoxicity events. See Section 6.2.1.3 for details on reporting AESI. Cardiac safety data will be collected up to 12 months after randomization in all patients.

Severity

Intensity of all AEs will be graded according to NCI-CTCAE v4.03 using Grades 1 to 5. Adverse events not listed on the NCI-CTCAE should be graded as mild to life-threatening as follows:

• Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
• Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity
• Grade 3	Severe	Inability to work or perform normal daily activity
• Grade 4	Life-threatening	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities
• Grade 5	Death	AE resulting in death

Relationship

The causal relationship between the study drug and the AE will be assessed by the Investigator as unrelated, unlikely to be related, possibly related, probably related, or unknown (unable to judge).

Adverse events can be classified as "unrelated" if there is not a reasonable possibility that the study drug caused the AE.

An "unlikely" relationship suggests that only a remote connection exists between the study drug and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the reported AE.

A "possible" relationship suggests that the association of the AE with the study drug is unknown; however, the AE is not reasonably supported by other conditions.

A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state or concomitant medication reactions) do not appear to explain the AE.

All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, e.g. because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.

An Adverse Drug Reaction is defined as all noxious and unintended responses to a medicinal product related to any dose.

An Unexpected Adverse Drug Reaction is defined as any adverse reaction, the nature of which is not consistent with the applicable product information.

The Investigator is responsible for recording all AEs observed during the study period. Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the study drug. The action taken and the outcome must also be recorded.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as a SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might be reported as an SAE.

Abnormal laboratory findings and other abnormal investigational findings

Abnormal laboratory findings and other abnormal investigational findings (e.g. on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g. anemia, increased ALT) – if it can be – must be reported as the AE rather than the abnormal value itself.

6.2.1.1 Reporting of Serious and Non-serious Adverse Events

Adverse events, serious and non-serious, will be collected from the time of informed consent and up to 30 days after the last dose of study drug at the Safety Follow-up Visit.

For all patients that have received at least 1 dose of study drug, all new non-cardiac, non-serious AEs (regardless of relatedness assessment) must be collected during the study through to the Safety Follow-up Visit.

For all patients who have received at least 1 dose of study drug, any clinical AE or abnormal laboratory test value that is *serious* (as defined in Section 6.2.1 above) and which occurs during the course of the study, regardless of the treatment arm, must be reported to the Sponsors within 1 working day of the Investigator becoming aware of the event (expedited reporting).

Related SAEs (cardiac and non-cardiac) MUST be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Any SAE, whether or not related to the study drug, must be reported immediately (within 24 hours of the study center's knowledge of the event) via Electronic Data Capture (EDC) at the center (details on reporting of SAEs are included in separate guidelines issued to each center).

The report will contain as much available information concerning the SAE to enable Quintiles to file a report, which satisfies regulatory reporting requirements. In addition to the initial 24-hour report, a completed, separate SAE Report form is to be sent to Quintiles Lifecycle Services within 48 hours of the event. If the SAE occurs in China, a Chinese version of the SAE Report form must be completed and signed by the Principal Investigator and sent to the Sponsor. All details on reporting of SAEs are included in separate guidelines issued to each center. These timelines apply to initial reports of SAEs and to all follow-up reports.

All SAEs will be recorded on the SAE Report form, the Adverse Events form in the eCRF, and source documents. Criteria for documenting the relationship to study drug as well as severity and outcome will be the same as those previously described.

All SAEs that are spontaneously reported within 30 days of a patient's last visit are to be collected and reported as previously described.

6.2.1.2 Reporting of Serious Adverse Events to Regulatory Agencies and Investigators

Investigators will be notified by the Sponsor or Quintiles of all SAEs that require prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee

(IEC). Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor or Quintiles. The Sponsor or Quintiles will ensure that all SAEs are reported to the appropriate Regulatory Agencies.

6.2.1.3 Reporting Adverse Events of Special Interest: Cardiac AEs

All cardiac AEs occurring during the study and up to 12 months after randomization in line with LVEF calculations, irrespective of causal relationship (unrelated, unlikely to be related, possibly related, probably related, or unknown) or severity (serious or non-serious), will be reported.

Symptomatic Left Ventricular Systolic Dysfunction

Symptomatic left ventricular systolic dysfunction should be reported as an SAE as CHF and not as individual signs and symptoms thereof. Congestive heart failure should be graded according to NCI-CTCAE Version 4.03 for "left ventricular systolic dysfunction" and the NYHA classification (see Appendix 2).

Asymptomatic Left Ventricular Systolic Dysfunction

In general, asymptomatic declines in LVEF should not be reported as AEs since LVEF data are collected separately in the eCRF. Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF to a value 10 percentage points below baseline or lower, and <50% must be reported as an AE
- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment must be reported in an expedited manner by using the SAE.

In both cases, it should be reported as left ventricular systolic dysfunction and graded according to NCI-CTCAE, v4.03.

6.2.1.4 Reporting Adverse Events of Special Interest: Infusion-related Reactions

Serious IRRs to the study drug infusion include dyspnea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema (see Section 5.6.2).

Patients should be informed about the potential occurrence of IRRs and be educated on how to contact the center staff if needed. **All patients will be closely monitored during the first cycle of administration.**

If an AE is considered to be an IRR by the Investigator, the AE should be reported with the event term “infusion-related reactions” and not as individual signs and symptoms. Signs and

symptoms should be entered in the appropriate part of the eCRF. Infusion-related reactions should be graded according to NCI-CTCAE v4.03.

6.2.1.5 Reporting Adverse Events of Special Interest: Hematotoxicity

Febrile neutropenia, leukopenia, anemia, thrombocytopenia and neutropenia have all been reported with infusions of the study drug.

Abnormal laboratory findings should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g. anemia, neutropenia) – if it can be – must be reported as the AE rather than the abnormal value itself.

6.2.1.6 Follow-Up of Adverse Events

Any AEs observed from the signing of informed consent up to 30 days after the last dose of study treatment (Safety Follow-up Visit) will be followed up to resolution. Resolution means that the patient has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE.

6.2.1.7 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST 1.1. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

Symptomatic clinical deterioration may occur in some patients. In this situation, progressive disease is evident in the patient's clinical symptoms but is not supported by the tumor measurements; or, the progressive disease is so evident that the Investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

6.2.1.8 Pregnancy

There are no clinical studies of trastuzumab or docetaxel in pregnant women; therefore, neither drug should be used during pregnancy. In female patients of childbearing potential, or male patients with partners of childbearing potential, appropriate contraceptive measures are mandatory during study treatment (e.g. barrier method [condoms, diaphragm]; intrauterine devices; surgical methods, or abstinence). Contraceptive measures are recommended for at least 7 months following the last dose of either trastuzumab or docetaxel.

A female patient who becomes pregnant during the study must be withdrawn from study treatment. The Investigator should report all pregnancies within 24 hours to the Sponsor or Quintiles. The Investigator should counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 7 months after the completion of study medication must also be reported to the Investigator.

It is not known whether trastuzumab or docetaxel is excreted in human milk. Women should be advised to discontinue nursing during study treatment and not to breastfeed for at least 7 months following the last dose.

6.2.2 Clinical Laboratory Evaluations

All local laboratory sample collection and testing will be scheduled as indicated in Table 4-1. Additional assessments may be performed as clinically indicated. Reference ranges for the local laboratory parameters must be supplied to the Sponsor or Quintiles before the study starts.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. The Investigator will evaluate any change in laboratory values and assess severity using NCI-CTCAE v4.03. Abnormal laboratory findings should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g. anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

The following routine safety tests will be performed at a local laboratory:

- Hematology (approximately 2 mL): hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with differential (neutrophils, lymphocytes,

monocytes, eosinophils, basophils and other cells). Additional tests may be performed per the institution's standard practice.

- Blood chemistry (approximately 3 mL): sodium, potassium, bicarbonate/carbon dioxide combining power, chloride, blood urea nitrogen/urea, calcium, uric acid, total protein, albumin, ALK, ALT (SGPT), AST (SGOT), gamma-glutamyl transpeptidase, lactate dehydrogenase, total bilirubin, creatinine, and non-fasting or fasting blood glucose (if possible a fasting glucose should be done at baseline). Additional tests may be performed per the institution's standard practice.

- Coagulation (approximately 2 mL): all patients will have INR and aPTT or PTT testing at baseline. Patients on therapeutic doses of anti-coagulants should have INR and aPTT or PTT measurements repeated during the study, at least before the start of every treatment cycle, and when clinically indicated.

- Pregnancy test: performed on women of childbearing potential via serum beta human chorionic gonadotropin at the beginning of the study (approximately 3 mL), before every third cycle, and at the Safety Follow-up Visit. Pregnancy tests will also be done via a urine test during the Treatment Period and up to 6 months after the Safety Follow-up Visit (see Table 4-1). If a urine test is positive, the pregnancy must be confirmed with a serum beta human chorionic gonadotropin test via the local laboratory.

- Urinalysis: all patients will have a urinalysis panel for standard tests before each cycle (including red blood cells, glucose, ketones, leukocytes, nitrites, pH, and proteins). For women of childbearing potential, a urine pregnancy test will be done before each cycle (when the serum test is not performed; see Table 4-1), then monthly for 6 months after the Safety Follow-up Visit. If a urine test is positive, the pregnancy must be confirmed with a serum beta human chorionic gonadotropin test via the local laboratory.

Laboratory assessments should be available prior to each administration of study drug for dose modification or delay requirements. During the Treatment Period, these assessments must be performed **within 3 days** prior to the administration of study drug at each cycle.

Screening blood samples: hepatitis B (HBcAb and HBsAg; if either is positive, HBV-DNA should be tested), hepatitis C (hepatitis C antibody and/or hepatitis C virus RNA should be tested), and HIV (approximately 6 mL), tested at a local laboratory.

The procedures for collecting and, if required, the storage and shipping of sample material are provided in the Laboratory Manual.

6.2.3 Vital Signs, Physical Findings and Other Safety Assessments

All assessments will be recorded in the eCRF.

6.2.3.1 Vital Signs

Vital signs will be measured in accordance with the schedule in Table 4-1 and will include sitting temperature, pulse, respiratory rate, and blood pressure.

6.2.3.2 Physical Examination

A symptom-directed physical examination will be performed with particular attention to cardio-vascular signs and symptoms in accordance with the schedule in Table 4-1.

Height and body weight will be measured at baseline. Weight will also be measured on Day 1 of every treatment cycle for confirmation of body surface area calculation (calculated by IWRS/IVRS at each cycle).

6.2.3.3 Electrocardiogram

A 12-lead ECG will be performed in accordance with the schedule in Table 4-1. Tracings will be collected while the patient is in supine or semi-recumbent position after having rested for 5 minutes.

6.2.3.4 Cardiac function

All patients must have their LVEF assessed by ECHO or MUGA in accordance with the Schedule of Events in Table 4-1. The same method must be used throughout the study period (ECHO is preferred because it can detect wall-motion abnormalities).

Calculations of LVEF are to be performed using the modified Simpson method or per local standard, and LVEF must be within normal range at baseline (within 42 days before randomization) as determined by the local facility before a patient can be enrolled in the study. The lower limit of normal for the LVEF facility will be reported along with the LVEF result.

6.3 Pharmacokinetics

In all patients, PK blood samples to determine serum trastuzumab concentrations (5 mL per sample) will be collected prior to infusion at Cycle 1 (at the time of blood sampling for assessment of hematology and baseline level of shed antigen), and starting at Cycle 3, prior to infusion, every 3 cycles (approximately every 9 weeks), at the same time as sample collections to assess for the presence of ADA/NADA while on treatment with HLX02 or Herceptin® (see also Section 6.4.1). The schedule of blood sampling for PK assessments is summarized in Table 6-1.

Additional blood samples for the determination of trastuzumab in serum will be collected in all enrolled patients. Compliance with PK sample collections, appropriate sample handling/processing/shipment as well recording of PK sampling information in the patients' eCRF (see below) will be closely monitored. The PK samples will be collected at the following time points:

- Cycle 1, Day 1, at the end of infusion
- Cycles 4 and 8, prior to infusion (at the time of blood sampling for assessment of hematology)
- Cycle 8, Day 1, at the end of infusion

In general, at the visits scheduled for assessment of clinical laboratories and PK, it is suggested that the samples be collected in the following order if possible: PK sample (then ADA/NADA sample if scheduled) then clinical laboratory samples.

Note: For all cycles with predose PK collections, trough trastuzumab levels will be defined as the PK samples collected at the time of the laboratory tests within a maximum of 3 days prior to Day 1 of the next cycle.

Note: The end-of-infusion samples on Day 1 of Cycles 1 and 8 must not be collected at the infusion site or from the same arm of the infusion site (e.g. if study drug is infused into the right arm, the PK sample must be collected from the left arm).

The following information will be documented in the eCRF: administered dose of HLX02 or Herceptin®, start/stop date and time of HLX02 or Herceptin® infusion of last cycle (i.e. prior to the sample collected for trastuzumab level analysis); date and time of each blood sample collected for trastuzumab analysis; and start/stop date and time of HLX02 or Herceptin® infusion on visit day.

Determination of concentrations of trastuzumab in serum will be performed by a Sponsor-contracted bioanalytical laboratory using validated analytical methods. The procedures for collecting, handling, storing and, if required, shipping of samples are described in a separate Laboratory Manual.

Table 6-1 Schedule of Blood Sampling for Pharmacokinetic and Immunogenicity Assessments

Cycle/Day	Visit Window (days)	Sampling for PK assessments	Sampling for ADA/NADA assessments	Shed Antigen
Cycle 1[2]	-7[1]	Pre-infusion (5 mL)		Pre-infusion (1.5 mL)
Cycle 1, Day 1[3]		End of infusion (5 mL)	-	-
Prior to Cycles 3, 6, 9, 12, and 15[2]	-3[1]	Pre-infusion (5 mL)		-
Prior to Cycles 4 and 8[3] (at the time of hematology sample collection)	-3[1]	Pre-infusion (5 mL)	-	-
Cycle 8, Day 1[3]		End of infusion (5 mL)	-	-
Safety Follow-up (30 ±2 days)	±2[4]	-	X (5 mL)	-

ADA = anti-drug antibodies; NADA = neutralizing anti-drug antibodies; PK=pharmacokinetic.

1. Prior to Cycle 1, samples for ADA/NADA, PK, clinical laboratory including hematology and shed antigen must be collected within 7 days before infusion. For subsequent cycles, PK and ADA/NADA samples, as appropriate, must be collected within 3 days before infusion.
2. PK and ADA/NADA time-matched samples while patients remain on treatment with HLX02 or Herceptin®: prior to infusion at Cycle 1, then starting at Cycle 3, prior to infusion every 3 cycles (approximately every 9 weeks).
3. Extended PK samples: end of infusion at Cycle 1, prior to infusion at Cycles 4 and 8, and end of infusion at Cycle 8.
4. The Safety Follow-up Visit will take place 30 (±2) days after last administration of docetaxel and/or after last administration of HLX02 or Herceptin®, whichever occurs last. A blood sample to test for antibodies against trastuzumab (ADA/NADA) will also be collected at the Safety Follow-up Visit.

Note: In general, at the visits scheduled for assessment of clinical laboratories and PK, it is suggested that the samples be collected in the following order if possible: PK sample (then ADA/NADA sample if scheduled) then clinical laboratory samples including hematology.

6.4 Other Assessments

6.4.1 Immunogenicity (Anti-drug Antibodies)

Blood samples (5 mL per sample) for testing of the incidence and titer of ADA against trastuzumab and the incidence of any NADA will be collected in all patients during the study in accordance with Table 6-1. A blood sample will be taken at the Safety Follow-up Visit to assess for the presence of ADA/NADA (along with blood sampling for routine laboratory tests).

Samples will initially be screened for antibodies. A confirmation assay will be used to confirm the positive status for samples which scored potentially positivity by the Screening assay. In confirmed positive samples, the relative titer of the antibody will be determined as well as whether the confirmed positive sample represent a neutralizing antibody.

The samples will be submitted to a Sponsor-contracted bioanalytical laboratory and measured using validated assays.

The procedures for collecting, handling, storing and, if required, shipping of ADA samples are described in a separate Laboratory Manual.

6.4.2 Tumor Samples (ER/PgR and HER2) at Screening

To be included in the study, patients must have a FFPE tissue block from the primary tumor or a metastatic lesion to confirm HER2-positivity;[11] if not available, a fresh biopsy sample will be collected. While a previous local IHC test with a score of IHC 2+ or 3+ can be used as a Prescreening evaluation to determine if a patient might be suitable, this will not be sufficient for enrollment. For a patient to be eligible, they must be HER2-positive as confirmed by the central laboratory using a FISH or IHC test, i.e. patients with a previous local IHC score of 2+ must be tested centrally by FISH and those patients with a previous local IHC score of 3+ must be confirmed centrally by IHC. HER2-positive is defined as an amplification ratio ≥2.0 if using FISH or a score of 3+ if using IHC. All results obtained from the central laboratory will be recorded in the eCRF.

Tumor tissue samples will be submitted in the form of either paraffin blocks or unstained, freshly cut slides containing formalin-fixed tumor tissue. Because uncontrolled oxidation processes on the slides may affect slides, tumor tissue blocks are preferred. However, if a tumor block is not available, 7-13 (depending on the tests required; please refer to the laboratory manual for more information) unstained freshly cut slides of 4 μm will be submitted (the number of slides submitted may be reduced pending on the regulatory and or IEC requirements of some countries). The slides must be sent to the central laboratory within 2 weeks of being cut. Slides sent to the central laboratory will not be returned to the institution from which they were sent.

Patients will be stratified before randomization by their tumor's hormonal status (ER and PgR), as determined by IHC either at a local or central laboratory. Other stratification factors include prior neo-/adjuvant therapy with Herceptin® and ethnicity (Asian and non-Asian).

The procedures for collecting, storage and shipping of sample material are provided in the Laboratory Manual.

6.5 Appropriateness of Measurements

Efficacy assessments are standard and reliable for an oncology study. The safety assessments are standard and relevant to the particular study drug and comparator being investigated.

7.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Central review of primary efficacy variable
- Center Initiation Visit
- Early center visits post-enrollment
- Routine center monitoring
- Ongoing center communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final Clinical Study Report (CSR).

In addition, Sponsor and/or Quintiles Clinical Quality Assurance Department may conduct periodic audits of the study processes, including, but not limited to study center, center visits, central laboratories, vendors, clinical database, and final CSR. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and Regulatory Agencies.

7.1 Monitoring

The Sponsor has engaged the services of a contract research organization, Quintiles, to perform all monitoring functions within this clinical study. Quintiles' monitors will work in accordance with Quintiles' SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study center, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent has been obtained from all patients correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study center. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each center while patients are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification). For the following items, this check will be 100%:

- Patient identification number
- Patient consent obtained
- Patient eligibility criteria (inclusion and exclusion criteria)
- Efficacy variables
- Medical record of AE.

For all other items, at least 70% of the data will be checked.

7.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of Quintiles.

Electronic Data Capture will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study center staff prior to the study being initiated and any data being entered into the system for any study patients.

All data must be entered in English. The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the patient's visit. To avoid inter-observer variability, every effort

should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the Principal Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study center staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the patient's medical history, that verify the existence of the patient, the inclusion and exclusion criteria and all records covering the patient's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each patient who receives study medication, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature.

If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using WHODRUG.

7.3 Quality Assurance Audit

Study centers, the study database and study documentation may be subject to a Quality Assurance audit during the course of the study by the Sponsor or Quintiles on behalf of the Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

8.0 STATISTICS

8.1 Determination of Sample Size

The difference in rate of ORR (Herceptin® - control) and its two-sided 95% confidence interval (CI) was calculated by pooling the results of the subgroup of patients with HER2-positive tumors defined as FISH positive or IHC 2+ and 3+, from 2 published randomized studies comparing ORR following treatment with Herceptin® + paclitaxel or equivalent, versus paclitaxel or equivalent alone (Genentech, 2010, Table 9;[12] Marty et al, 2005,[8] Table 2). Using the Der Simonian-Laird[14] estimate random effect model, the difference in ORR and its 95% CI was estimated to be 0.2493 [0.1579; 0.3407]. The metabin function of the meta library of the R language[15] was used to implement this estimate. An equivalence limit marginally tighter than the lower bound of this confidence interval is used as the criterion of equivalence: [-0.1350, 0.1350]. Given the published ORRs for ITT populations in Marty et al[6] (61%), CLEOPATRA[10] (69%), and HERITAGE[16] (64%) trials, a conservative rate of 60% ORR_{24} was assumed for the ITT population. A sample size of 289 evaluable patients per arm was calculated to yield 84% power to show equivalence using the above equivalence limits [-0.1350, 0.1350] with the two-sided 95% CI for the difference in ORR_{24} HLX02-Herceptin® in the ITT population. Assuming a 5% dropout rate, the number of patients required to be randomized is approximately 304 per arm. Swain et al[17] have approximately 8% patients discontinuing who would be excluded from a PP population. Based on this, a 10% drop in patients is assumed in the PP population, compared to the ITT population, making a total of approximately 15% dropout in the PP population. It is assumed that 3% of ITT patients with ORR fail to be included in the PP population (e.g. due to protocol deviations other than early discontinuation). Under these assumptions the denominator for ORR will decrease by 10%, compared to that of the ITT population, but the number of ORRs will decrease by only 3%. It is thus assumed there will be a higher rate of 65% ORR_{24} in the PP population. With these assumptions, 304 patients per arm will yield a sample size for the PP population of approximately 258 and the study will have 80% power to show equivalence in the PP population.

A blinded sample size re-estimation procedure is planned after the primary efficacy data at Week 24 are available in the first 300 patients (see Section 8.9.1).

8.2 Statistical Methods

Baseline characteristics of the patient sample will be described using summary statistics. All estimates will be reported with standard deviation or 95% CI. All analyses, summaries, and listings will be performed using SAS® software (9.4 or higher). Full details of the statistical analysis methods will be provided in the Statistical Analysis Plan.

8.2.1 Data for Analysis

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the Statistical Analysis Plan prepared by Quintiles and approved by the Sponsor before database lock. The statistical analysis will be performed by Quintiles.

8.2.2 Analysis Populations

Definitions for each analysis population include:

- Safety population will comprise all patients who have received study drug once and have at least 1 safety assessment post-treatment.
- Intent-to-treat (ITT) population will comprise all patients who were randomized.
- Per-protocol (PP) population will comprise all patients who have at least 8 cycles of treatment and have at least 1 tumor measurement after treatment, or discontinued treatment early due to Investigator-assessed disease progression or excessive toxicity, and do not have major protocol deviations/violations.
- Pharmacokinetic population will comprise all patients who received study drug and who have at least 1 measured concentration at a scheduled PK time point after the start of study drug without any protocol deviations or events which may affect the PK results.

8.2.3 Missing Data

The Investigator will make all possible effort to ensure that most patients will undergo at least 1 tumor assessment during the first 8 cycles of treatment and patients are followed for survival until 12 months after randomization.

For the primary efficacy analysis of the ITT population, patients who discontinued for any reason before a response was documented at least once will be counted as non-responders.

For the PP efficacy analysis, patients for whom the efficacy endpoint is missing, i.e. patients without at least 1 valid post-treatment evaluation, are excluded from the PP Population, except those who are withdrawn due to toxicity, early progression or death, in which case the patients will be classified as non-responders.

Sensitivity analyses to assess the robustness of conclusions to missing data will be carried out if there are more than 5% of patients missing evaluations in either treatment arm. Sensitivity analyses will include an analysis that assumes that outcomes are missing at random. Such an analysis is likely to be conservative in the context of assessing equivalence because under the missing-at-random assumption missing outcomes tend to reflect any differences between treatment groups found in the observed outcomes. In addition, results of a pattern-mixture

model will be presented where, for patients discontinuing due to an AE, the probability of ORR is assumed to be reduced by some clinically-plausible constant (a "delta-adjustment"[18]). Further details of the method for dealing with missing data and of the implementation of the sensitivity analyses will be described in the Statistical Analysis Plan.

8.3 Patient Disposition

The disposition summary will include all enrolled patients.

8.4 Patient Characteristics

Patient characteristics will be summarized as described in the Statistical Analysis Plan.

8.5 Efficacy Analyses

8.5.1 Primary Analyses

The primary endpoint is ORR_{24}, calculated as the proportion of patients with a best response of CR or PR from first assessment up to Week 24 according to RECIST 1.1. Equivalence will be concluded if the two-sided 95% CI of the difference in the 2 proportions is completely contained within the interval [-0.1350; 0.1350]. Two-sided 95% CIs for the difference between the 2 treatment arms in ORR_{24} will be presented, controlling for randomizing stratification factors using Mantel-Haenszel weights for the strata.

The ITT population will be considered the primary population for the efficacy analyses. Repeat analyses using the PP population will explore robustness of results; the robustness to missing data of conclusions from the ITT analysis will be assessed via sensitivity analyses.

8.5.2 Secondary Analyses

Overall objective response at Week 6, 12, 18, and 24 by CIR will be analyzed in a similar way to that of the primary endpoint to show the pattern of response.

For time-to-event secondary endpoints (DoR, PFS up to 12 months and OS at 12, 24, and 36 months), Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics (i.e. the probability of being event-free) and corresponding two-sided 95% CIs. The CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice.[19] The estimate of the standard error will be computed using Greenwood's formula. A Cox model will be used to compare the hazard ratio (HR). The point estimates and 95% CIs of the HR will be reported. Binary secondary endpoints (DCR and CBR) will be analyzed in a similar way to that of the primary endpoint except that ratios

will be estimated, controlling for randomizing stratification factors through a log binomial model.

8.5.3 Subgroup Analyses

Any subgroup analyses will be exploratory (post hoc) in nature. The details of these analyses, if any, will be described in the Statistical Analysis Plan.

8.6 Safety

All safety variables will be summarized using the safety population at the post-baseline evaluation during the Treatment Period.

8.6.1 Adverse Events

Treatment-emergent adverse events are defined as AEs that first occurred or worsened in severity after the first administration of the study drug. Adverse event summaries will include incidence of treatment-emergent AEs by MedDRA preferred term and system organ class, SAEs including deaths, AEs that led to study drug discontinuation, AESI, and AEs by maximum severity (graded according to NCI-CTCAE v4.03) and relationship to study drug.

8.6.2 Clinical Laboratory Evaluations

Laboratory assessments will be presented as mean changes from baseline and incidence of abnormal values. Shift tables will be presented for selected parameters.

8.6.3 Vital Signs Measurements, Physical Findings and Other Safety Evaluations

Vital signs, LVEF and other safety evaluations will be summarized. Shift tables will be presented for selected parameters.

8.7 Immunogenicity

Immunogenicity results, including overall ADA results (Screening, confirmatory, and titers, as appropriate), NADA results, and the time course of antibodies (defined as the time to first post-dose observation of a positive ADA response) will be listed. The number and percent of patients testing positive for ADA or NADA will be summarized by treatment over time. If applicable, the time to interconversion of antibodies may be summarized by treatment using appropriate descriptive statistics.

8.8 Pharmacokinetic Analyses

Trastuzumab concentrations in serum will be summarized descriptively by study population, treatment and scheduled collection time. Exposure to trastuzumab will be further evaluated

with respect to specific disease characteristics such as baseline levels of shed antigen and correlated with tumor response and major safety findings.

Additional PopPK modeling and/or correlation between trastuzumab exposure and response (safety, immunogenicity and/or efficacy) data may be evaluated separately, as appropriate. If performed, a separate analysis plan will be prepared and results will be reported separately from the clinical study report.

8.9 Interim Analyses

8.9.1 Blinded Sample Size Re-estimation

After 300 patients have been evaluated for response at Week 24, the pooled ORR_{24} will be calculated, and a blinded sample size re-estimation procedure will take place to ensure at least 80% power using the conditional power from the observed ORR difference and adjusting considering the actual dropout rate observed during this period. The procedure will be overseen by a Data Monitoring Committee (DMC).

Details on the procedure and the formulae to be used will be documented in the Statistical Analysis Plan.

8.9.2 Data Monitoring Committee

A DMC will be established to oversee the blinded sample size re-estimation procedure; to review safety data at regular intervals in order to safeguard the interests of study participants; and to monitor the overall conduct of the study. Responsibilities of the DMC will be fully documented in the DMC Charter.

8.9.3 Database Locks and Clinical Study Reports

Once response assessment data at Week 24 are available for all patients, there will be a first database lock and the designated unblinded study team will conduct analyses on the primary efficacy data, as well as PK, safety/immunogenicity and survival data, up to Week 24, for submission of a CSR to the relevant Regulatory Agencies. The results will only be shared with a small number of study members who are not involved in the direct running of the study itself. All Investigators, site teams, and patients will remain blinded for the rest of the Treatment Period (up to 12 months after the last patient randomized), which is when the second database lock will occur.

At the time of the second database lock, a separate CSR with all efficacy, PK, safety and survival data up to 12 months for all patients will be submitted to the relevant Regulatory Agencies.

The final database lock will occur 36 months after the last patient randomized in order to report final OS data to the relevant Regulatory Agencies.

9.0 ETHICS

9.1 Institutional Review Board or Independent Ethics Committee

An Ethics Committee should approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will provide the contract research organization, Quintiles (on behalf of the Sponsor), with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study center(s). The Investigator should submit the written approval to Quintiles before enrollment of any patient into the study.

The Sponsor should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to Quintiles of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of patients or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

9.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki, the applicable guidelines of ICH for GCP and the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

9.3 Patient Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient will be entered into the study. The ICF contains a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time. Written consent must be given by the patient and/or legal representative, after the receipt of detailed

information on the study. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The Investigator is responsible for ensuring that informed consent is obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study medication. The Investigator will provide each patient with a copy of the signed and dated consent form.

10.0 STUDY ADMINISTRATION

10.1 ADMINISTRATIVE STRUCTURE

Study monitoring, pharmacovigilance, data management, biostatistics and medical writing, and vendor management will be performed by the contract research organization, Quintiles. Cenduit will be responsible for randomization via IWRS/IVRS. Medical monitoring will be shared by the Sponsor and Quintiles. Drug supplies will be the responsibility of a third party vendor. Both central and local laboratories will be used.

10.2 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study site should plan on retaining such documents for approximately 15 years after study completion. The study site should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any study records.

Any documents that would lead to a breaking of the blind must only be accessible to the designated unblinded team until the official unblinding occurs.

10.3 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each patient randomized into the study.

The Investigator will allow the Sponsor, Quintiles, and authorized Regulatory Agencies to have direct access to all documents pertaining to the study, including individual patient medical records, as appropriate.

10.4 Investigator Information

10.4.1 Investigator Obligations

This study will be conducted in accordance with the ICH-GCP; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

10.4.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 1). By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH-GCP and applicable regulatory requirements. The study will not be able to start at any center where the Investigator has not signed the protocol.

10.4.3 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

10.5 Financing and Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study. The terms of the insurance will be kept in the study files.

11.0 REFERENCES

1 International Agency for Research on Cancer. Available from: URL http://globocan.iarc.fr/Pages/fact_sheets_population.aspx; Globocan 2012. Accessed 2015 Nov.

2 Contractor KB, Kaur K, Rodrigues GS, Kulkarni DM, Singhal H. Male breast cancer: is the scenario changing. World J Surg Oncol. 2008 Jun; 6:58.

3 Speirs V, Shaaban AM. The rising incidence of male breast cancer. Breast Cancer Res Treat. 2009 May; 115(2):429-30.

4 Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987 Jan; 235(4785):177-82.

5 Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989 May; 244(4905):707-12.

6 Cooke T, Reeves J, Lanigan A, Stanton P. HER2 as a prognostic and predictive marker for breast cancer. Ann Oncol. 2001; 12(1):S23-8.

7 Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001 Mar; 344(11):783-92.

8 Marty M, Cognetti F, Maraninchi D, Synder R, Mauriac L, Tubiana-Hulin M et al. Randomized Phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer administered as first-line treatment: the M77001 Study Group. J Clin Oncol. 2005 Jul; 23(19):4265-74.

9 Herceptin Product Information. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000278/WC500074922.pdf. Accessed 2016 May.

10 Baselga J, Cortés J, Kim S-B, Im SA, Hegg R, Im YH et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012; 366:109-19.

11 Wolff AC, Hammond MEH, Hicks DG, Dowsett M, McShane LM, Allison KH et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013 Nov; 31(31):3997-4013.

12 Genentech. Final labeling text, Herceptin; 2010. Available from: URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf Accessed 2017 Mar.

13 Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-

based clinical practice guideline. American Society of Clinical Oncology. J Clin Oncol. 2006 Jul; 24(19):3187-205.

14 Der Simonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 7 (3). 1986:177–188.

15 R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria; 2012.

16 Hope SR, Barve A, Waller CF, Hernandez-Bronchud M, Herson J, Yuan J et al. Heritage: A phase III safety and efficacy trial of the proposed trastuzumab biosimilar Myl-1401O versus Herceptin. J Clin Oncol. 2016; 34(suppl; abstr LBA503).

17 Swain SM, Baselga J, Kim S-B, Ro J, Semiglazov V, Compone M et al. Pertuzumab, trastuzumab, and docetaxel in HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2015; 372:724-34.

18 O'Kelly M and Ratitch B. Clinical trials with missing data: a guide for practitioners. John Wiley & Sons, Ltd. Chichester, United Kingdom; 2014.

19 Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. John Wiley & Sons, Inc. New York, United States of America; 1980.

12.0 APPENDICES

APPENDIX 1: SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: Double-blind, Randomized, Multicenter, Phase III Clinical Study to Compare the Efficacy and to Evaluate the Safety and Immunogenicity of Trastuzumab Biosimilar HLX02 and EU-sourced Herceptin® in Previously Untreated HER2-Overexpressing Metastatic Breast Cancer

PROTOCOL NO: HLX02-BC01

This protocol is a confidential communication of Shanghai Henlius Biotech, Inc.
I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Shanghai Henlius Biotech, Inc.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to Quintiles.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

APPENDIX 2: NYHA

When there is a reasonable uncertainty that the symptoms or signs are not of cardiac origin, the diagnosis should be *No heart disease.*

Functional Capacity	**Objective Assessment**
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

*The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

APPENDIX 3: ECOG PERFORMANCE STATUS

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance 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, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

APPENDIX 4: RECIST 1.1

See attached guidelines.

Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R et al. *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)*. Eur J Cancer. 2009; 45:228-247
[internet: http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf]