PROTOCOL

A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, PHASE III STUDY OF THE EFFICACY AND SAFETY OF HERCULES PLUS TAXANE VERSUS HERCEPTIN® PLUS TAXANE AS FIRST LINE THERAPY IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

Compound Name: Hercules (trastuzumab)

US IND Number (if applicable): N/A

EudraCT No: 2011-001965-42

Indication: For the first-line treatment of Human Epidermal Growth Factor Receptor 2 positive (HER+) metastatic breast cancer

Protocol No: MYL-Her 3001

Phase: III

Protocol version and date: Amend 6; Version 9.0; 10 April, 2015

Global Amendment

Sponsor Signatory: MYLAN GmbH
Thurgauerstrasse 40
CH-8050 Zurich, Switzerland
Tel: ++41-(0)44-308 7575
Fax: ++41-(0)44-308 7520

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Document History

<table>
<thead>
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<tr>
<td>Amendment 6, Version 9.0 Global Amendment</td>
<td>10 April, 2015</td>
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<td>Original protocol</td>
<td>07 February, 2012</td>
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All revisions made to date are incorporated in this amendment, including those requested by Regulatory Authorities (RA), Ethics Committee (EC)/Institutional Review Board (IRB), etc.
SIGNATURE PAGE

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<td>MYL-Her 3001</td>
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<td>A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, PHASE III STUDY OF THE SAFETY AND EFFICACY OF HERCULES PLUS TAXANE VERSUS HERCEPTIN® PLUS TAXANE AS FIRST LINE THERAPY IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER</td>
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I, the undersigned, have read this protocol and confirm that to the best of my knowledge the protocol accurately describes the planned conduct of the study and has been reviewed and endorsed by the Clinical Operations, Clinical Development, Safety and Statistics, and Regulatory Leads for this trial.

Dr. Rasmus Rojkjaer  
Vice President, Head of Global Biologies R&D  
Mylan GmbH

Dr. Eduardo Pennella  
Senior Director, Clinical Project Leader  
Mylan Inc

Dr. Rajiv Sharma  
Senior Director, Global Head Clinical Safety  
Global Product Safety & Risk Management  
Mylan, UK

Jack Nyberg  
Senior Manager, Biostatistician  
Mylan Inc

Manfred Kurz  
Senior Manager, Regulatory and Biologics  
Mylan

Date

20/04/15

18 - APR - 2015

17 - APR - 2015

17 Apr 2015

Date
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## PROTOCOL SYNOPSIS

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<th>Hercules</th>
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<td>Protocol Number</td>
<td>MYL-Her 3001</td>
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<tr>
<td>EudraCT Number</td>
<td>2011-001965-42</td>
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<td>Phase III</td>
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### Protocol Title and Purpose

A multicenter, double-blind, randomized, parallel-group, Phase III study of the efficacy and safety of Hercules plus taxane versus Herceptin® plus taxane as first line therapy in patients with HER2-positive metastatic breast cancer.

The purpose of Part 1 of the study is to compare the efficacy and safety of Hercules plus docetaxel or paclitaxel (i.e., taxane) versus Herceptin® plus taxane in patients who have not received previous first line treatment for Human Epidermal Growth Factor Receptor 2 positive (HER2+) metastatic breast cancer (MBC).

The purpose of Part 2 of the study is to continue to evaluate safety and immunogenicity of Hercules and Herceptin® given as a single agent.

### Indication

For the first-line treatment of Human Epidermal Growth Factor Receptor 2 positive (HER2+) metastatic breast cancer

### Planned Study Sites

Approximately 200 global sites are anticipated to participate.

### Objectives and Endpoints: Part 1

**Primary:** To compare the independently assessed best overall response rate (ORR) (according to Response Evaluation Criteria in Solid Tumor [RECIST] 1.1 criteria) at Week 24 with Hercules in combination with taxane versus Herceptin® plus taxane in patients who have not received previous first line treatment for HER2+ MBC.

**Secondary:**

- To compare independently assessed clinical activity at Week 24 between treatment arms by measuring: time to tumor progression (TTP); progression-free survival (PFS); overall survival (OS); duration of response (DR).
- To descriptively compare the safety, immunogenicity, and tolerability profile of Hercules and Herceptin® given in combination with a taxane.
- To compare the immunogenicity of Hercules and Herceptin® by examining the clinical immunogenic response;
- To compare the population pharmacokinetic (PopPK) area under the curve (AUC), maximum drug concentration (Cmax), minimum drug concentration (Cmin), clearance, volume of distribution (Vd), and T1/2, profiles of Hercules and Herceptin®.

**Exploratory:** To assess the impact of shed extracellular domain fragments of the HER2 receptor (HER2/extracellular domain [ECD]) in serum on pharmacokinetic (PK), and efficacy parameters.

### Objectives and Endpoints: Part 2

**Primary:**
- To continue to evaluate the safety and tolerability profile of Hercules and Herceptin® given as a single agent.
- To compare the immunogenicity of Hercules and Herceptin® by examining the clinical immunogenic response;

**Secondary:** To compare the clinical activity at Week 48 between treatment arms by measuring: PFS, OS and DR, and OS at 36 months or after 240 deaths, whichever occurs first, as observed from the time of randomization.

### Study Design

**Part 1:** A multicenter, double-blind, randomized, parallel-group, Phase III study to compare the efficacy and safety of Hercules plus taxane versus Herceptin® plus taxane in patients with HER2+ MBC. Either docetaxel or paclitaxel (Investigator site level choice) is planned for at least 24 weeks until documented response to therapy, disease progression, or discontinuation. Disease response and progression will be assessed locally by the Investigator on the basis of clinical and radiographic evidence using RECIST 1.1 criteria. The primary and secondary efficacy analyses will be performed using independently assessed radiographic evidence for the Intent-to-Treat (ITT) population. The primary analysis population for best ORR will be those patients who had measureable disease at baseline and for the secondary endpoint, DR, only those who are responders will be included in the analysis.

**Part 2:** A multicenter, double-blind, parallel-group study to continue to compare the safety and immunogenicity and efficacy of Hercules versus Herceptin® in patients with HER2+ MBC who have clinical benefit to first-line combination therapy with a taxane. All patients who have at least stable disease (SD), will continue with either single agent Hercules or Herceptin® alone until death, unacceptable toxicity or disease progression.

**Population pharmacokinetics:** During Part 1 of the study, for both the Hercules and Herceptin® treatment arms, PK sampling for C\text{min} and C\text{max} (end of infusion) will be collected for all patients. A PopPK subset, with sufficient samples available to perform the necessary analysis of PopPK modeling will be used to assess AUC, C\text{max}, C\text{min}, clearance, V\text{d}, and T\text{1/2} at various time points in the PopPK. Patients randomized into the main study will sign an additional consent form for the PopPK subset. We anticipate that approximately 80 patients will need to be enrolled in this subset collection in order to obtain sufficient samples for analysis.

**Long term survival follow-up:** OS for this treated population will be determined with every 3 month follow-up until either 240 deaths or 36 months, whichever occurs first, as observed from the time of randomization.

**Exploratory evaluations:** In addition, during Part 1 of the study, blood samples will be collected in all patients to assess the impact of soluble shed HER2/ECD on PK and efficacy at pre-dose on Cycles 1, 3, 5, 7, and end of treatment (EOT). Additional samples (ECD) will be obtained on Cycles 9, 13 and every 4 cycles thereafter, EOT and end of study (EOS) for continued evaluation of immunogenicity in patients continuing to receive therapy. A blood sample will be obtained on Cycle 1, Day 1, to be used for assay development and validation.
Planned Number of Patients

Up to 600 patients may be randomized into the study in a 1:1 ratio of the two treatment groups (See sample size determination).

Study Entry Criteria

**Inclusion criteria:**

1. ≥18 years of age.
3. Locally recurrent or MBC that is not amenable to curative surgery and/or radiation.
4. Documentation of HER2 gene amplification by fluorescent in situ hybridization (FISH) (as defined by a ratio >2.0) or documentation of HER2-overexpression by immunohistochemistry (IHC) (defined as IHC3+, or IHC2+ with FISH confirmation) based on the sponsor-identified central laboratory prior to randomization. Archival tumor tissue samples can be used.
5. Documentation of estrogen receptor/progesterone receptor (ER/PgR) status (positive or negative) based on either a local or central laboratory report must be available before randomization.
6. Pathologically confirmed breast cancer with at least one measurable metastatic target lesion (based on RECIST criteria, version 1.1). Bone, central nervous system (CNS), and skin lesions, as well as lesions that were irradiated, biopsied or had any form of local intervention or surgical manipulation are only to be assessed as non-target lesions. Baseline imaging studies of target lesions must have been performed and submitted for central confirmation in the 4 weeks preceding randomization.
7. Patients with a history of CNS metastases or cord compression are eligible if they have been successfully treated and are off steroids for at least 4 weeks before first dose of investigational product. Patients with newly detected CNS metastases must be successfully treated (e.g., radiotherapy, stereotactic radiosurgery) before being considered for the trial. Patients with known or suspected brain metastases must undergo a baseline brain computed tomography (CT) or magnetic resonance imaging (MRI).
8. Patients previously treated with trastuzumab or lapatinib in the adjuvant setting are allowed if metastatic disease was diagnosed at least one year after the last dose of treatment.
9. Prior treatment with hormonal agents or bisphosphonates/denosumab is allowed. Bisphosphonates/denostumab can be given simultaneously with study treatment but cannot start after randomization and is considered an indication of progressive disease (PD). Hormonal agents must be discontinued prior to beginning study therapy.
11. Screening laboratory values within the following parameters:
   - Absolute neutrophil count ≥1.5 x 10⁹/L (1500/mm³),
   - Platelet count ≥100 x 10⁹/L (100,000/mm³),
   - Hemoglobin ≥9.0 g/dL (90 g/L) without a prior transfusion in the last 2 weeks,
   - Serum creatinine ≤1.5 x ULN (upper limit of normal),
- Total bilirubin $\leq 1.0 \times$ ULN ($>1.0 \times$ ULN if documented Gilbert’s disease),
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN,
- AST and/or ALT $<1.5 \times$ ULN if alkaline phosphatase $>2.5 \times$ ULN,
- Alkaline phosphatase $>2.5 \times$ ULN; if bone metastases present and no liver dysfunction present.

12. Left ventricular ejection fraction (LVEF) within institutional range of normal as measured by multiple gated acquisition scan or echocardiogram.

13. The patient is willing to comply with the protocol and procedures for the duration of the study, including all scheduled visits and examinations.

14. The patient is either not of childbearing potential or is willing to practice birth control by using two different highly effective methods of contraception, or abstain from sexual intercourse for the duration of the study and follow-up. In particular, patients of childbearing potential must:
- Female patients are to use a method which results in less than 1% failure rate per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence, or vasectomized partner. Have a negative human chorionic gonadotropin serum pregnancy test at screening and by urinary test on Day 1.
- Male patients without vasectomy are required to use a condom with spermicide and their female partner to use another form of contraception.

15. Written informed consent signed by the patient or her legal representative (if patient is unable to provide) prior to any study-related procedures not standard of care.

**Exclusion criteria:**

1. Prior systemic therapy in the metastatic disease setting. This includes: chemotherapy, signal transduction inhibitors (e.g., lapatinib), HER2 targeted therapy (e.g., trastuzumab), or other investigational anticancer therapy.

2. Prior treatment with neoadjuvant or adjuvant anthracyclines with a cumulative dose of doxorubicin of $>400$ mg/m$^2$, epirubicin dose $>800$ mg/m$^2$.

3. Participation in the active treatment phase of an investigational drug study $\leq 28$ days prior to randomization.

4. Patients with bone or skin as the only site of disease. Patients with skin lesions measurable by CT scans or MRI as only site of measurable disease are allowed.

5. Surgery or radiotherapy $\leq 2$ weeks preceding Day 1. Target lesions have to be outside the irradiated fields and the patient has fully recovered from surgery or radiotherapy.
6. Presence of unstable angina or a history of congestive heart failure according to the New York Heart Association criteria, history of myocardial infarction <1 year from randomization, clinically significant valvular disease, serious cardiac arrhythmia requiring treatment, uncontrolled hypertension or known pulmonary hypertension.

7. Peripheral sensory or motor neuropathy Grade 2 or higher according to the National Cancer Institute-Common Terminology Criteria (NCI-CTC) Version 4.03 [19].

8. Any other cancer, including contralateral breast cancer, within 5 years prior to screening with the exception of adequately treated ductal carcinoma in situ, adequately treated cervical carcinoma in situ, or adequately treated basal or squamous cell carcinoma of the skin.

9. Immunocompromized patients, including known seropositivity for human immunodeficiency virus, or current or chronic hepatitis B and/or hepatitis C infection (as detected by positive testing for hepatitis B surface antigen or antibody to hepatitis C virus with confirmatory testing).

10. Patients with documented severe hypersensitivity reaction to trastuzumab, paclitaxel, docetaxel or excipients used in their formulations, including murine protein remnants and patients with hereditary fructose intolerance.

11. Evidence of significant medical illness (including dyspnea at rest or serious pulmonary illness, etc.) or abnormal laboratory finding that, in the Investigator’s judgment, will substantially increase the risk associated with the patient’s participation in, and completion of, the study, or could preclude the evaluation of the patient’s response.

Investigational Product

<table>
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<th>Name: Hercules</th>
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<td><strong>Dose, route, frequency:</strong> 8 mg/kg loading dose at the start of treatment by continuous intravenous (I.V.) infusion over 90 min (± 10 minutes). Thereafter, (beginning 3 weeks after the loading dose) 6 mg/kg dose by continuous I.V. infusion over 30 min (± 10 minutes) every 3 weeks until discontinuation.</td>
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Reference Product

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<th>Name: Herceptin®</th>
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<td><strong>Dose, route, frequency:</strong> 8 mg/kg loading dose at the start of treatment by continuous I.V. infusion over 90 min (± 10 minutes). Thereafter (beginning 3 weeks after the loading dose) 6 mg/kg dose by continuous I.V. infusion over 30 min (± 10 minutes) every 3 weeks until discontinuation.</td>
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Treatment Regimen

| Part 1: Hercules plus taxane or Herceptin® plus taxane will be administered for a minimum of 8 treatment cycles (1 treatment cycle = 3 weeks based on trastuzumab administration) unless the patient experiences unacceptable side effects, disease progression or is prematurely withdrawn from treatment (see Section 9.1). Tumor assessments are to be conducted every 6 weeks (± 3 days) until Cycle 8 and every 12 weeks (± 3 days) Cycle 9 and beyond independent of delays in treatment administration. Choice of taxane will be made by the Investigator at each study site prior to the start of screening and will apply to all patients enrolled by that site. |
Docetaxel 75 mg/m² will be administered as an I.V. infusion over 1 hour (± 10 minutes) on Day 1 of a 3 week cycle, except in Cycle 1 when docetaxel will be given on Day 2.

OR

Paclitaxel 80 mg/m² will be administered as an I.V. infusion over 1 hour (± 10 minutes) on Day 1, except in Cycle 1 when paclitaxel will be given on Day 2. Paclitaxel is administered weekly during each cycle. At the discretion of the Investigator, one administration of paclitaxel may be omitted every 4 weeks.

**NOTE:** Beginning in Cycle 2 and for each cycle thereafter in Part 1, taxane treatment should be administered 30 minutes (± 10 minutes) after completing the Hercules or Herceptin® infusion.

Patients who discontinued taxane due to toxicity and receive Hercules or Herceptin® as a single agent in Part 1 may continue to do so at the Investigator’s discretion, if they are receiving clinical benefit but have not achieved a complete response (CR)/partial response (PR) after 8 cycles of treatment. Patients receiving single agent Hercules or Herceptin® in Part 1, after 24 weeks will move into Part 2 of the study if patient has at least SD.

**Part 2:** All patients who have at least SD in Part 1 will continue with either Hercules alone or Herceptin® alone (i.e., the study treatment which they have been using in study Part 1, without taxane) until disease progression, unacceptable toxicity or death.

Patients who have not achieved CR or PR after 8 cycles of therapy (SD) are able to continue at the Investigator’s discretion to receive taxane plus Hercules or Herceptin® in Part 1 of the study or discontinue the taxane and start Part 2 of the study (see Section 9.1). Tumor assessments are to be conducted every 12 weeks (± 3 days) independent of delays in treatment administration.

After a patient discontinues the study, the patient should be treated according to the discretion of the Investigator (documented in electronic data capture [EDC]) and patients will be minimally followed for OS every 3 months from the date of randomization for up to 36 months, until 240 deaths, whichever occurs first.

### Criteria for Evaluation

**Primary efficacy endpoint:** The primary efficacy endpoint is the best ORR where objective response is defined as a CR or PR according to RECIST 1.1 (see Appendix A) based on centralized review evaluation achieved at 24 weeks after start of treatment. Only patients with measurable disease at baseline will be included in the analysis of objective response.

**Secondary efficacy endpoints:**
- TTP is defined as the time from randomization to the date of first documentation of objective progression.
- PFS is defined as the time from randomization to the first documentation of objective progression or death from any cause.
- OS is defined as the time from date of randomization until the date of death from any cause.
- DR is defined as the time from first documentation of objective response to the date of first documentation of objective progression or death due to any cause.

**Population pharmacokinetic outcome variables:**
- Estimates of AUC, Cmin and Cmax to assess the similarity of Hercules versus Herceptin®, using descriptive statistics.
- Descriptive PopPK analysis on key parameters for Hercules and for Herceptin® (half-life, clearance, central and peripheral distribution volumes) over the initial 24 weeks (Part 1).
- To assess the potential impact of soluble HER2/ECD antigen on trastuzumab PK levels and efficacy parameters.

**Safety outcome variables:**
- Nature, frequency and severity of the reported adverse events (AEs),
- Laboratory assessments,
- Vital signs,
- Electrocardiogram (ECG),
- LVEF,
- Immunogenicity.

### Statistical Methods

**Sample size determination:** Final sample size may be up to 600 patients randomized. The rationale is described in the following paragraphs.

A sample size of 410 patients (205 per treatment group) from Protocol Amendment 2 and beyond is required to provide at least 80% power to declare Hercules equivalent to Herceptin® in the analysis of ORR at Week 24. This sample size assumes that both treatment groups will exhibit an ORR of 69% at Week 24 and that the ratio of Hercules to Herceptin® will be analyzed with a two-sided 90% confidence interval (CI). If the 90% CI falls wholly within an equivalence region defined as (0.81, 1.24), then equivalence will be declared.

The equivalence region was justified by performing a fixed-effects meta-analysis with historical randomized Herceptin® trials to estimate the treatment effect of Herceptin plus chemotherapy versus chemotherapy alone.

To arrive at the planned number of patients, the initial required sample size of 410 was increased to 456 to reflect an approximate 10% attrition rate. It is expected that, at most, 10% of the randomized patients in Protocol Amendment 2 and beyond will be lost-to-follow-up.

Final sample size will be determined at the interim analysis using the sample size re-estimation approach described in the SAP and may increase up to 600.

**Analysis populations:** The following 4 analysis populations are planned for this study:
Intention-to-treat (ITT) population: All patients randomized.

Safety Population (SAF): All patients who had received at least one dose of Hercules/Herceptin®.

Per-protocol (PP) Population: All patients in the ITT population who started treatment without major protocol deviations as defined in the statistical analysis plan (SAP) and finally decided upon in a blinded data review meeting before the database lock for study Part 1. In particular, patients will be excluded from the PP population if they: have anti-trastuzumab antibodies at baseline; drop-out for reasons other than PD with less than 2 complete cycles of therapy received; have no post-baseline tumor assessment.

Pharmacokinetic (PK) population: All patients who receive at least one dose of allocated study medication and who provide at least one post-dose concentration sample for PopPK analysis.

The primary efficacy analysis will be based on the ITT population of patients in Protocol Amendment 2. The efficacy evaluation in the PP set and the full ITT set (which is comprised of all randomized patients) will also be reported in sensitivity analyses. The PopPK analysis will be based on the PK populations. The analysis of safety will be based on the SAF Population.

Primary Efficacy Analysis:

Part 1: The ratio of the best ORRs at Week 24 within the ITT population of patients in Protocol Amendment 2 will be statistically compared with the following hypotheses:

Ho: $\frac{RT}{RC} \leq 0.81$ or $\frac{RT}{RC} \geq 1.24$

H1: $0.81 < \frac{RT}{RC} < 1.24$,

where RT and RC are the best ORR of Test (Hercules) and Control (Herceptin®), respectively.

A two-sided 90% CI for the ratio of the best ORRs will be calculated based on the method of logarithmic transformation with no adjustment for covariates. The two-sided 90% CI is equivalent to two one-sided tests at the 5% level. Equivalence will be declared if the CI is completely within the equivalence range of (0.81, 1.24).

Part 2: No primary efficacy analyses are declared in Part 2.

Stratification: Patients will be stratified by:

- Tumor progression into metastatic phase ≥2 years OR <2 years after primary diagnosis (calculated as time from primary tumor surgery until randomization). Patients diagnosed with primary metastatic disease will be classified together with the patients who progressed <2 years, regardless of the date of tumor surgery.
- ER/PgR status (ER and/or PgR positive/ER and PgR negative).
- Type of taxane received (e.g., paclitaxel or docetaxel). Investigator’s discretion at the site level prior to the start of screening.

Secondary Efficacy Analysis:

Part 1: The following time-to-event secondary endpoints will be analyzed in the same manner at Week 24:
• TTP assessed by the Independent Central Review (ICR),
• PFS, assessed by ICR,
• OS.

For each of the above endpoints, Kaplan-Meier plots by treatment will be presented and the log-rank test of the two treatment groups unadjusted for any covariates will be performed. Cox’s proportional hazards model will be used to analyze for treatment effects, adjusting for each of the stratification factors. Hazard ratios and 95% CIs will be presented.

ORR, assessed by Investigator, will be analyzed in the same manner as the primary endpoint and used in sensitivity analysis.

**Part 2:** The following secondary efficacy endpoints will be analyzed in the same manner at Week 48:
• PFS, assessed by ICR,
• DR, assessed by ICR,
• OS,
• OS at 36 months or after 240 deaths from the time of randomization.

For each of the above endpoints, Kaplan-Meier plots by treatment will be presented and the log-rank test of the two treatment groups unadjusted for any covariates will be performed. Cox’s proportional hazards model will be used to analyze for treatment effects, adjusting for each of the stratification factors. Hazard ratios and 95% CIs will be presented. For DR, only responders will be included in the analysis.

**Long-Term Survival Follow-Up:** Long-term survival will be assessed at the end of the long-term survival follow-up period. Long-term survival will be analyzed in the same manner as TTP.

**Sensitivity Analyses:** The following sensitivity analyses will be performed on the primary endpoint, ORR:
• Subgroup analyses by age, ethnic origin, time from initial diagnosis of metastatic disease, previous adjuvant/neoadjuvant chemotherapy or HER2 targeted treatment and geographic region as detailed in the SAP.
• Cochran-Mantel-Haenszel analysis stratified by the stratification factors will be performed. Estimates of the relative risk and the odds ratio, and their 90% and 95% CIs will be presented.
• Logistic regression analysis of the treatment odds ratio adjusted for the stratification factors will be performed.
• The primary efficacy analysis will be replicated in the PP population as part of sensitivity analysis.
• The primary efficacy analysis will be replicated in the full ITT set (which is comprised of all randomized patients).
Sensitivity analyses for the secondary endpoints of PFS, OS, and DR will also be conducted (e.g., PFS at Week 24, assessed by the Investigator). Description of these analyses and any other sensitivity analyses will be described in the SAP.

**Interim Analyses:** A formal interim analysis will be overseen by the data and safety monitoring board when at least 30% of the information target is available. The sample size will be re-estimated at this analysis based on the interim data. In addition, the futility analysis will be carried out. The study may be stopped for futility if pre-specified futility boundaries are met, The details will be described in the SAP.

**Multiple Comparison Adjustments:** No multiple comparison adjustment for the Part 1 primary analysis is required. All other efficacy analyses in Part 1 or 2 will not be adjusted for multiplicity.

**Population Pharmacokinetics:** The population analysis will be performed with NONMEM, Version 7.2, or later (Icon Solutions). The final population estimates will be presented in a table with their variability according to the most appropriate assumptions retained during model building. Model building will start from published population analyses using a two-compartment model.

- **Graphical exploration:** A graphical exploration of the concentration versus time data will be conducted to provide a visual inspection of the kinetic profile of Herceptin® versus Hercules and to guide the modeling process.
- **Structural pharmacokinetic model:** Consistent with the literature, a two-compartment linear model will be described with parameters of clearance, $V_d$ of the central compartment, inter-compartmental clearance, and $V_d$ for the peripheral compartment. Further model development will be performed as appropriate.
- **Models for inter-individual (level 1) and residual variability (level 2) random effects:** Inter-individual variability in clearance and volume terms will initially be assigned log-normally distributed random effects. Model appropriateness will be evaluated. An attempt to add IIV to additional structural parameters will be explored, but may not be feasible based on the sparseness of the data. Residual variability will be modeled initially with a constant coefficient of variation model.
- **Covariate model:** Potentially influential covariates will be evaluated using a forward selection followed by backward elimination process. The evaluated covariates may include alkaline phosphatase, number of metastatic sites, ECD, and body weight.
- Maximum likelihood estimates model: First-order conditional estimation methods will be used initially for parameter estimation. Individual patient empiric Bayesian parameter estimates will be produced for each model parameter with inter-individual variability included in the model. PK parameters reflecting exposure to drug (AUC, C_{max}, C_{min}, clearance, V_d, and terminal elimination half-life) will be reported for each patient in the PopPK. Only descriptive and exploratory statistics are planned; the conceptual framework for bioequivalence trials will not be applied formally, as this is a secondary endpoint and 100% bioavailability is assumed for I.V. agents.

Safety Analyses: The safety analyses will be based on the SAF population. Treatment-emergent adverse events (TEAEs), defined as AE{s} which started or deteriorated after the first administration of investigational medicinal product (IMP) but on or within 28 days following the last dose of the IMP. TEAEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Serious AE{s} (SAEs) and AE{s} will be summarized by System Organ Class and Preferred Term and analyzed overall as well as according to severity and relationship to the IMP.

Descriptive summaries of observed values and change from baseline will be presented for clinical laboratory evaluations (hematology and biochemistry) by treatment arm. Assessments of laboratory variables according to clinical relevance and NCI-CTC grades will be tabulated by visit and treatment arm for each clinical laboratory parameter in frequency tables. Additionally, for each laboratory parameter, shifts in value from baseline to all post-baseline visits will be presented by treatment arm in shift tables.

The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter by treatment arm (frequency tables). Additionally, for each of these urine parameter shifts in assessments from baseline to all post-baseline visits will be presented for each treatment arm (shift tables).

For vital signs, ECG, and LVEF descriptive summaries of observed values and changes from baseline will be presented by visit and treatment arm. In addition, ECG frequency and shift tables will be presented for the classified values of QTc (Bazett and Fridericia) as described in International Conference on Harmonization E14 (ICH-E14), as well as for the overall clinical assessment.

Study and Treatment Duration

The sequence and maximum duration of the study periods will be:

**Screening:** Up to 4 weeks, 28 days.

**Study Part 1** (Hercules or Herceptin® plus taxane): at least 8 cycles.

**Study Part 2** (Hercules or Herceptin® alone) until progression, discontinuation (see Section 9.1) or death.
| The maximum planned study duration for Part 1 and Part 2 of the treatment period is approximately 52 weeks which is the median PFS for first line treated MBC patients. The overall study duration for Part 1 and Part 2 is expected not to exceed 37.9 months (~163 weeks) which corresponds to the median OS for first line treated MBC. Primary and secondary endpoints will be analyzed at Week 24 in Part 1 and at Week 48 in Part 2 of the study. |
SCHEDULE OF ACTIVITIES

The Schedule of Activities tables provide an overview of the protocol visits and procedures. Refer to Study Procedures (Section 7) and Assessments (Section 10) for detailed information about each procedure and assessment.

### Table 1  Schedule of Activities Part 1

<table>
<thead>
<tr>
<th>GREY FIELDS: To be done PRIOR to dosing at specified time point</th>
<th>Screen. ≤28 days</th>
<th>Part 1 - Combined Treatment: Hercules and Taxane or Herceptin® and Taxane®&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cycle 1 - Cycle 2 W3 Day 22 Cycle 3 W6 Day 43 Cycle 4 W9 Day 64 Cycle 5 W12 Day 85 Cycle 6 W15 Day 106 Cycle 7 W18 Day 127 Cycle 8 W21 Day 148 Cycle 9 SD W24 Every 3 weeks Cycle 10 SD W27 Every 3 mo follow-up to 36 mo EOT&lt;sup&gt;c&lt;/sup&gt; EOS&lt;sup&gt;d&lt;/sup&gt; Every 3 mo follow-up to 36 mo</td>
</tr>
<tr>
<td>Informed consent</td>
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<td></td>
</tr>
<tr>
<td>Demographic data</td>
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<td></td>
</tr>
<tr>
<td>Medical and breast cancer history</td>
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<td></td>
</tr>
<tr>
<td>Physical examination including vital signs</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight (plus height on W0 only)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor burden (RECIST)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CT/MRI of chest and upper abdomen&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Left Ventricle Ejection Fraction (LVEF) by ECHO&lt;sup&gt;3&lt;/sup&gt; or MUGA</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Immunohistochemistry (IHC) and/or fluorescent in situ hybridization (FISH)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>GREY FIELDS: To be done PRIOR to dosing at specified time point</td>
<td>Screen.</td>
<td>Part 1 - Combined Treatment: Hercules and Taxane or Herceptin® and Taxane®&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td></td>
<td>s28 days</td>
<td>Cycle 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td>ER/PgR Determination</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum chemistry</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Coagulation (PT/PTT/INR)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Immunogenicity&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dipstick urine analysis</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test (from serum on screening and from urine thereafter)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Randomization within 3 days prior to Day 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Samples for C&lt;sub&gt;max&lt;/sub&gt; for all patients&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Samples for C&lt;sub&gt;max&lt;/sub&gt; for all patients&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Additional samples for PopPK for patients in the PopPK subset&lt;sup&gt;6&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sample for exploratory analysis</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Samples for soluble ECD fragments</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Taxane premed according to local SOC&lt;sup&gt;7&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dosing of Hercules or Herceptin®</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
GREY FIELDS: To be done PRIOR to dosing at specified time point

<table>
<thead>
<tr>
<th>GREY FIELDS: To be done PRIOR to dosing at specified time point</th>
<th>Screen. Part 1 - Combined Treatment: Hercules and Taxane and Herceptin® and Taxanea,d,e</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6</th>
<th>Cycle 7</th>
<th>Cycle 8</th>
<th>Cycle 9 SD</th>
<th>Every 3 mo follow-up to 36 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration of docetaxel Day 1 or weekly paclitaxelf</td>
<td>≤ 28 days</td>
<td>Cycle 1</td>
<td>Cycle 2</td>
<td>Cycle 3</td>
<td>Cycle 4</td>
<td>Cycle 5</td>
<td>Cycle 6</td>
<td>Cycle 7</td>
<td>Cycle 8</td>
<td>Cycle 9 SD</td>
<td>Every 3 mo follow-up to 36 mo</td>
</tr>
<tr>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 8</td>
<td>Day 22</td>
<td>Day 43</td>
<td>Day 64</td>
<td>Day 85</td>
<td>Day 106</td>
<td>Day 127</td>
<td>Day 148</td>
<td>Day 169</td>
<td>X</td>
</tr>
<tr>
<td>Adverse eventsg</td>
<td>throughout the study</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Survival follow-up upon discontinuation of study treatmenth,i</td>
<td>throughout the study</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

C<sub>max</sub> = maximum drug concentration; C<sub>min</sub> = minimum drug concentration; CT = computed tomography; ECD = extracellular domain (of HER2); ECG = electrocardiogram; ECHO = echocardiogram; EOS = end of study; EOT = end of treatment; ER/PgR = estrogen receptor/progesterone receptor; INR = international normalized ratio; mo = month; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; SD= stable disease; SOC = standard of care; PopPK = population pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; Screen. = screening; W = week.

a For all cycle visits there is a grace period of +/- 3 days for scheduling these visits. Study treatment cycles should be scheduled with respect to the previous cycle.
b Randomization will only be performed upon written informed consent and fulfilling all eligibility criteria and no more than 3 days prior to Cycle 1, Day 1.
c Do not perform EOT visit at end of Part 1 for patients continuing onto Part 2. EOT should be performed at the time patients discontinue treatment.
d The following procedures are performed locally throughout the study – hematology, chemistry, coagulation, urinalysis, pregnancy testing.
e The following procedures are performed centrally throughout the study – Her2, ER/PgR, PK, immunogenicity, exploratory analysis, ECG.
1: At baseline, central confirmation of imaging is required prior to randomization. The imaging method used at baseline to assess a specific lesion must be used throughout the study to consistently assess the lesion according to RECIST 1.1 criteria. Activities associated with tumor burden (including bone scan) must be completed within 28 days prior to dosing on Cycle 1, Day 1. If patient screen fails, rescreen must be completed within 42 days of original screening visit date, tumor burden must be completed within 28 days of randomization. Tumor assessments are to be conducted every 6 weeks (± 3 days) independent of delays in treatment administration in Part 1 (up to Cycle 8) and conducted every 12 weeks (± 3 days) independent of delays in treatment administration Cycle 9 and beyond.
2: Except for baseline imaging, to be performed earlier if clinically indicated. CT/MRI of brain for patients with brain involvement and bone scans if bone involvement and can be repeated during the study, if clinically indicated. Contact the Medical Monitor if baseline bone scan has been performed outside the 28 day screening window. Bone scan must be repeated if beyond 42 days from projected Cycle 1, Day 1 visit. Confirmatory x-rays should be obtained at baseline and at each tumor assessment thereafter of lesions on bone scan that are consistent with metastatic disease.
3: ECHO is preferred; same methodology is to be used throughout study. Repeat at least every 3 weeks if 16% absolute decrease in LVEF from pre-treatment levels or LVEF below institutional level of normal and a 10% absolute decrease in LVEF, and also consult with Medical Monitor. ECHO or MUGA to be performed every 6 months after the EOT visit for 24 months.
4: Immunogenicity blood sample collection includes: anti-drug antibody (ADA). If patient develops hypersensitivity reaction, obtain ADA and PK blood sample at the time of reaction.
5: One pre-dose sample (Cmin) in all patients Cycles 1, 2, 4, 6, 8 and 9; 1 post dose sample Cycle 1 and Cycle 6. If unable to obtain at Cycle 6 sample may be obtained at any Cycle 7 - 9.
6: One post-dose sample (Cmax) at Cycle 4. In addition to the two random samples at Day 2 and Day 8, two more random samples should be taken at any two unscheduled visits during Cycles 2 - 8. Samples should be taken prior to taxane administration.
7: Premedication according to the local SOC for taxane (see appropriate SmPC for guidance). If to be administered Cycle 1, Day 1 should be administered after Herceptin® infusion is completed.
8: Beginning with Cycle 2, Day 1 and on Day 1 for every cycle thereafter in Part 1; docetaxel or paclitaxel should be administered 30 minutes (± 10 minutes) after completion of the Hercules or Herceptin® infusion; paclitaxel is given weekly; docetaxel is given on Day 1 only of each cycle. At the discretion of the Investigator, 1 dose of paclitaxel may be omitted every 4 weeks.
9: All SAEs will be recorded from time ICF is signed until EOS visit and should be followed until resolution or deemed stable. Should an Investigator be made aware of any SAE occurring any time after the active reporting period, the SAE (in case of reasonable causality) must be reported to Mylan within 24 hours. AEs will be collected from the first dose of study drug administration until the EOS visit.
10: All medication given within 3 weeks prior to screening and until EOS. All pharmacological and radiological therapy for breast cancer at any time until EOS.
11: Survival follow-up every 3 months by telephone call until death or 36 months from the date of randomization have elapsed. Confirm continued use of contraception at the first 2 contacts for survival follow-up, i.e. 7 months after last dose of blinded trastuzumab.
12: At Cycle 9 patients with at least SD will proceed to Part 2. Patients with disease progression or unacceptable toxicity should proceed to EOT assessments. This decision is based on clinician’s decision of local assessments.
14: In Cycle XS; X denotes next consecutive numerical cycle, e.g., 10, 11, etc.
15: Perform EOS assessments 28 days (+/- 7 days) after last dose of study treatment.
16: Obtain tumor assessments (RECIST, CT/MRI scan), cardiac function, immunogenicity, and ECD samples at Cycle 13 and every 4 cycles thereafter.
17: Obtain if not performed within prior 6 weeks (2 cycles).
## Table 2  Schedule of Activities Part 2

<table>
<thead>
<tr>
<th>GREY FIELDS: To be done PRIOR to dosing at specified time point</th>
<th>Part 2 - Single Treatment with Hercules or Herceptin&lt;sup&gt;a,b,c&lt;/sup&gt;</th>
<th>Cycle 9 W24 Day 169</th>
<th>Cycle 10 W27 Day 190</th>
<th>Cycle 11 W30 Day 211</th>
<th>Cycle 12 W33 Day 232</th>
<th>Cycle 13 W36 Day 253</th>
<th>Cycle 14 W39 Day 274</th>
<th>Cycle 15 W42 Day 295</th>
<th>Cycle 16 W45 Day 316</th>
<th>Cycle XR11 W48 Day 337</th>
<th>EOT</th>
<th>EOS&lt;sup&gt;12&lt;/sup&gt;</th>
<th>Every 3 mo follow-up to 36 mos&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
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<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>ECOG performance status</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Tumor burden (RECIST)&lt;sup&gt;1&lt;/sup&gt;</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>X&lt;sup&gt;12&lt;/sup&gt;</td>
<td>X&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>CT/MRI of chest and upper abdomen&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;12&lt;/sup&gt;</td>
<td>X&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Left Ventricle Ejection Fraction (LVEF) by ECHO or MUGA&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X</td>
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<td></td>
<td></td>
<td>X&lt;sup&gt;12&lt;/sup&gt;</td>
<td>X</td>
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<tr>
<td>ECG</td>
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<td></td>
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<td>X&lt;sup&gt;12&lt;/sup&gt;</td>
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<tr>
<td>Hematology</td>
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<td>Serum chemistry</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Coagulation (PT, PTT, INR)</td>
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<td>X</td>
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<td>Immunogenicity&lt;sup&gt;4, 8&lt;/sup&gt;</td>
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<td>Dipstick urine analysis</td>
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<tr>
<td>Samples for Cmin for all patients</td>
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<td>Pregnancy test (from urine)</td>
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<td></td>
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<td>X</td>
</tr>
<tr>
<td>Administration of Hercules or Herceptin&lt;sup&gt;6&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Survival follow-up upon discontinuation of study treatment&lt;sup&gt;3&lt;/sup&gt;</td>
<td>throughout the study</td>
<td></td>
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<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Adverse events&lt;sup&gt;7&lt;/sup&gt;</td>
<td>throughout the study</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup> HERCULES (trastuzumab).

<sup>b</sup> Every 3 mos from Cycle 9.

<sup>c</sup> HEART failure.

<sup>1</sup> CT/X-ray.

<sup>2</sup> MRI.

<sup>3</sup> ECHO.

<sup>4</sup> Serum.

<sup>5</sup> ECOG.

<sup>6</sup> ECHO.

<sup>7</sup> PT/PTT.

<sup>8</sup> Immunogenicity.

<sup>9</sup> MUGA.

<sup>10</sup> Cmin.

<sup>11</sup> ECOG.

<sup>12</sup> Survival follow-up upon discontinuation of study treatment.
**GREY FIELDS: To be done PRIOR to dosing at specified time point**

<table>
<thead>
<tr>
<th>Cycle 9</th>
<th>Cycle 10</th>
<th>Cycle 11</th>
<th>Cycle 12</th>
<th>Cycle 13</th>
<th>Cycle 14</th>
<th>Cycle 15</th>
<th>Cycle 16</th>
<th>Cycle XR</th>
<th>EOT</th>
<th>EOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>W24</td>
<td>W27</td>
<td>W30</td>
<td>W33</td>
<td>W36</td>
<td>W39</td>
<td>W42</td>
<td>W45</td>
<td>W48</td>
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</tr>
</tbody>
</table>

Concomitant medication and procedures:

- **CT =** computed tomography; **ECD =** extracellular domain (of HER2); **ECG =** electrocardiogram; **ECOG =** Eastern Collaborative Oncology Group; **ECHO =** echocardiogram; **EOS =** end of study; **EOT =** end of treatment; **mo =** month; **MRI =** Magnetic Resonance Imaging; **MUGA =** Multiple Gated Acquisition Scan; **PopPK =** population pharmacokinetics; **W =** week.

1. For all cycle visits there is a grace period of +/- 3 days for scheduling these visits. Study treatment cycles should be scheduled with respect to the previous cycle.
2. The following procedures are performed locally throughout the study – hematology, chemistry, coagulation, urinalysis, pregnancy testing.
3. The following procedures are performed centrally throughout the study – Her2, ER/PgR, PK, ECD, immunogenicity, exploratory analysis, ECG.
4. The imaging method used at baseline to assess a specific lesion must be used throughout the study to consistently assess the lesion according to RECIST 1.1 criteria. Bone scan only if clinically indicated. Tumor assessments are conducted every 12 weeks (± 3 days) independent of delays in treatment administration in Part 2.
5. To be performed earlier if clinically indicated. CT/MRI of brain for patients with brain involvement and bone scans if bone involvement and can be repeated during the study, if clinically indicated.
6. ECHO is preferred; same methodology is to be used throughout study. Repeat at least every 3 weeks if 16% absolute decrease in LVEF from pre-treatment levels or LVEF below institutional level of normal and a 10% absolute decrease in LVEF and also consult with Medical Monitor. ECHO or MUGA to be performed every 6 months after the EOT visit for 24 months.
7. Obtain tumor assessments, cardiac function, immunogenicity, and ECD samples at Cycle 13 and every 4 cycles thereafter.
8. Survival follow-up every 3 months by telephone call until death or 36 months from date of randomization. Confirm continued use of contraception at the first 2 contacts for survival follow-up, i.e. 7 months after last dose of blinded trastuzumab.
9. In Cycle XR; X denotes next consecutive numerical cycle, e.g., 17, 18, etc.
10. Obtain tumor assessments (RECIST, CT/MRI scan), cardiac function, immunogenicity, and ECD samples at Cycle 13 and every 4 cycles thereafter.
LIST OF ABBREVIATIONS

ADA Anti-drug antibody
ADR Adverse drug reaction
AE Adverse event
ALT Alanine aminotransferase
ANC Absolute neutrophil count
AR Adverse reaction
AST Aspartate aminotransferase
AUC Area under the curve
BSA Body surface area
CHF Congestive heart failure
CI Confidence interval
C\text{max} Maximum drug concentration
C\text{min} Minimum drug concentration
CNS Central nervous system
CR Complete response
CRA Clinical research associate
CSR Clinical study report
CRF Case report form
CT Computed tomography
CTC AE Common Terminology Criteria for Adverse Events
CV Curricula vitae
CYP450 Cytochrome P450
DR Duration of response
DSMB Data and safety monitoring board
EC Ethics committee
ECD Extracellular domain (of HER2)
ECG Electrocardiogram
ECHO Echocardiogram
ECOG PS Eastern Cooperative Oncology Group performance status
eCRF Electronic case report form
EDC Electronic data capture
EORTC European Organization for Research and Treatment of Cancer
EOS End of study
EOT End of treatment
ER/PgR Estrogen receptor/Progesterone Receptor
EU European union
FDA Food and Drug Administration
FISH Fluorescent \textit{in situ} hybridization
GCP Good Clinical Practice
hCG Human chorionic gonadotropin
HER2+ Human epidermal growth factor receptor 2 positive
IB Investigator’s Brochure
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICF</td>
<td>Informed consent form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IgG1</td>
<td>Immunoglobulin G1</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
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<tr>
<td>ILN</td>
<td>Institutional level normal</td>
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<tr>
<td>IMP</td>
<td>Investigational medicinal product</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
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<tr>
<td>I.V.</td>
<td>intravenous</td>
</tr>
<tr>
<td>IVRS</td>
<td>Interactive voice response system</td>
</tr>
<tr>
<td>IWRS</td>
<td>Interactive web response system</td>
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<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>MBC</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MUGA</td>
<td>Multiple gated acquisition scan</td>
</tr>
<tr>
<td>NCI-CTC</td>
<td>National Cancer Institute-Common Terminology Criteria</td>
</tr>
<tr>
<td>NOEL</td>
<td>No observable effect level</td>
</tr>
<tr>
<td>ORR</td>
<td>Overall response rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-free survival</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
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<tr>
<td>PopPK</td>
<td>Population pharmacokinetics</td>
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<tr>
<td>PP</td>
<td>Per protocol</td>
</tr>
<tr>
<td>PR</td>
<td>Partial Response</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>PTT</td>
<td>Partial thromboplastin time</td>
</tr>
<tr>
<td>RA</td>
<td>Regulatory Authorities</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumor</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAF</td>
<td>Safety population</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SD</td>
<td>Stable disease</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of product characteristics</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected unexpected serious adverse reaction</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment-emergent adverse events</td>
</tr>
<tr>
<td>TK</td>
<td>Toxicokinetics</td>
</tr>
<tr>
<td>TTP</td>
<td>Time to tumor progression</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>V_d</td>
<td>Volume of distribution</td>
</tr>
</tbody>
</table>
1  INTRODUCTION

1.1  BACKGROUND

Breast cancer is the most common malignancy among women in the Western hemisphere and the commonest cause of cancer death in women worldwide [1, 2]. Rates vary by about five-fold around the world, but are increasing in regions that until recently had low rates of the disease [1].

The Human Epidermal Growth Factor Receptor-2 (HER2)/neu oncogene is a tyrosine kinase transmembrane receptor amplified in human breast cancer [3]. It is a member of the erbB-like oncogene family, and is related to the epidermal growth factor receptor [3, 8, 30]. Overexpression of HER2 has been observed in up to 20% - 30% of primary breast cancers [4]. Patients with HER2/neu gene amplification and HER2 protein overexpression are a more aggressive phenotype with an associated poorer prognosis [5, 6, 7, 8].

Trastuzumab (Herceptin®, Roche) is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody against HER2. Trastuzumab binds to subdomain IV of the HER2 extracellular domain (ECD) and exerts its antitumor effects by blocking HER2 cleavage [9], stimulating antibody dependent, cell-mediated cytotoxicity [10] and inhibiting ligand-independent, HER2-mediated mitogenic signaling [11]. Treatment with the anti-HER2 humanized monoclonal antibody trastuzumab used in combination with chemotherapy (e.g., paclitaxel [Taxol®, BMS] or docetaxel [Taxotere®, Sanofi Aventis]), as compared with chemotherapy alone, significantly improves progression-free survival (PFS) and overall survival (OS) among patients with HER2-positive (HER2+) metastatic breast cancer (MBC) [12, 13]. Herceptin® has also been used in clinical trials as monotherapy for patients with MBC who have tumors that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease (Herceptin® alone).

Generally, trastuzumab is well tolerated. [14] Adverse effects include non-target-related chills and fever and (rarely) hypotension during the initial infusion. In randomized clinical trials, infections were seen at a higher frequency in the trastuzumab group versus the chemotherapy only group (47% versus 29% respectively). Cardiac dysfunction presenting as congestive heart failure (CHF) is seen more commonly when trastuzumab is administered with anthracyclines, and less frequently when it is administered with cyclophosphamide or paclitaxel. However, patients who develop cardiotoxicity while receiving trastuzumab therapy alone generally improve once use the agent is discontinued. [15] Overall, trastuzumab is associated with a threefold increase in Grade 3 or 4 cardiac toxicity, and careful monitoring of ejection fraction is warranted. [16, 17, 18]

Hercules is being developed by Mylan as a biosimilar trastuzumab to Herceptin®. This single pivotal Phase III study is being conducted to compare the efficacy and safety between Hercules and the European Union (EU) reference product, Herceptin®, when used as primary treatment for first line HER2+ MBC. The first part of the study will
evaluate both treatments in combination with docetaxel or paclitaxel, and the second part of the study will evaluate continued treatment with Hercules or Herceptin® alone in those patients who have responded to first line therapy.

Mylan GmbH is developing Hercules (Bmab-200), as a similar biological medicinal product to Herceptin®. Hercules the investigational medicinal product (IMP) described in this protocol contains the proposed active biosimilar substance trastuzumab (Herceptin®, developed by Genentech/Roche).

A biosimilar approach has been employed throughout the Hercules development program, which depends on the demonstration of comparability to the EU reference product, Herceptin® from the perspective of chemical, pharmaceutical, and biological attributes. Herceptin®, used throughout the comparability program, has been granted a marketing authorization in all major markets based on a complete quality, safety and efficacy data set.

Hercules was engineered by recombinant DNA technology to encode a monoclonal antibody, which is 100% identical in amino acid sequence to the heavy chain and light chain of the trastuzumab sequence. The molecule is produced in a recombinant Chinese Hamster Ovary cell line to obtain the glycosylated monoclonal antibody. The physico-chemical properties of Hercules have been evaluated in detail using state of the art orthogonal analytical methods.

Two comparative non-clinical studies were undertaken in cynomolgus monkeys to compare the pharmacokinetic (PK) profile after a single dose (25 mg/kg) and the toxicokinetics (TK) after multiple weekly doses (25 and 50 mg/kg). The PK serum profile, the calculated PK parameters, and the TK accumulation pattern were similar for Hercules and Herceptin®, suggesting a relative bioavailability above 80% of Hercules relative to Herceptin®. In vitro assays showed that the specific potency of Hercules was comparable to Herceptin® thus confirming similar pharmacological activities. As expected for a monoclonal antibody, and as already demonstrated for Herceptin®, the toxicity findings at all levels (systemic, local, histopathological) were very modest, and comparable between Hercules and Herceptin®. The no observable effect level (NOEL) was estimated to be at 50 mg/kg for both antibodies. No immunogenicity was detected.

In addition, a safety pharmacology study was conducted utilizing human cardiomyocytes as an in vitro model for the study of drug induced cardiotoxicity.

As Hercules is to be investigated in comparison with the EU reference product Herceptin®, therefore both treatments will be dosed according to the Herceptin® Summary of Product Characteristics (SmPC). As recommended in the Herceptin® European SmPC, this study proposes to administer both Hercules and Herceptin® at a starting dose of 8 mg/kg trastuzumab over 90 min by continuous intravenous (I.V.) infusion followed by 6 mg/kg trastuzumab over 30 min continuous I.V. infusion every 3 weeks.
To date, Phase I studies either completed or being conducted include:

**MYL-Her1001**: A Phase I, single center, single dose, 2-period, randomized, double-blind, cross-over study was conducted in 22 healthy Swiss male volunteers using Hercules and EU-approved Herceptin® as comparator. The patients either received the test drug (Hercules) or the reference drug (Herceptin®) in a cross-over design. The primary objective of the study was to ascertain PK bioequivalence of Hercules and Herceptin® after 8 mg/kg as a single I.V. dose infused over 90 min. Bioequivalence is established if the 90% confidence interval (CI) of the mean ratio of Hercules to Herceptin® meets the standard bioequivalence criteria of 80 - 125% for the area under the serum concentration curve from 0 to infinity (area under the curve [AUC]0-inf) and maximum observed serum concentration (Cmax).

The secondary objectives were to assess comparative systemic safety and tolerability including local tolerance, and to evaluate immunogenicity with anti-drug antibody (ADA) formation. In summary, The PK objectives of this study were achieved and Hercules can be considered as bioequivalent to the reference drug, Herceptin®, when administered as an 8.0 mg/kg I.V. infusion. Both Hercules and the reference drug Herceptin® had similar safety profiles and were well tolerated in this healthy male population. With regard to local site reaction there were only 2 patients (one in each group) who reported Grade 1 reactions by Draize scale. There was no decrease of cardiac function as evidenced by echocardiography. Lastly, there were no detectable ADAs.

**MYL-Her1002**: An investigational new drug application for authorization of a double blind, comparative 3–arm PK bioequivalence study (Study title: A single-center, randomized, double-blind, 3-arm, parallel-group Phase I study to compare the PK profiles of Hercules and Herceptin® (EU and US sourced) administered as a single I.V. infusion to healthy male volunteers”) in healthy volunteers has been submitted to the United States (US) Food and Drug Administration (FDA) to assess the similarity between Hercules and US as well as EU licensed Herceptin®. The objective of the study is to assess the 3-arm bioequivalence between the test products, EU sourced Herceptin® and US sourced Herceptin. On 07 December 2012 the FDA approved the conduct of the study.

### 1.2 RATIONALE

Drug cost accounts for an increasingly large proportion of health care expenditure, especially for patented biotechnology-derived medicines.

In the EU, drug cost is growing faster than any other component of health care expenditure. Therefore, the EU directive 2004/27/EC called for increased access to generic medicines.

The US is taking similar measures with the implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), a section of the Patient Protection and Affordable Care Act. The BPCI Act establishes an abbreviated approval pathway for
biological products demonstrated to be “highly similar” (biosimilar) to or “interchangeable” with a biological product already licensed by the FDA.

Mylan is developing Hercules to meet this global regulatory mandate to make biosimilar medicines available. Hercules is being developed as a cost-effective, biosimilar treatment option to the reference product Herceptin®.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

Part 1: To compare the independently assessed best overall response rate (ORR) (according to Response Evaluation Criteria in Solid Tumor [RECIST] 1.1 criteria) at Week 24 with Hercules plus taxane versus Herceptin® plus taxane in patients who have not received previous first line treatment for HER2+ MBC.

Part 2: The primary objective is to descriptively compare the safety, immunogenicity, and tolerability profile of single agent Hercules and Herceptin® and; to compare the immunogenicity of Hercules and Herceptin® by examining clinical immunogenic response.

2.2 SECONDARY OBJECTIVES

Part 1 of the study:

- To compare independently assessed clinical activity at Week 24 between treatment arms by measuring: time to tumor progression (TTP); progression-free survival (PFS); overall survival (OS); duration of response (DR).
- To descriptively compare the safety, immunogenicity, and tolerability profile of Hercules and Herceptin® given in combination with a taxane.
- To compare the populations pharmacokinetic (PopPK) AUC, $C_{\text{max}}$, minimum drug concentration ($C_{\text{min}}$), clearance, volume of distribution ($V_d$), and $T_{1/2}$, profiles of Hercules and Herceptin®.

Part 2 of the study:

- To compare the clinical activity at Week 48 between treatment arms by measuring: PFS, OS and DR, and OS at 36 months or after 240 deaths, whichever occurs first, as observed from the time of randomization.

2.3 EXPLORATORY OBJECTIVES

To assess the impact of shed ECD fragments of the HER2 receptor (HER2/ECD) in serum on PK and efficacy parameters.
3 STUDY DESIGN

3.1 DESCRIPTION OF OVERALL STUDY DESIGN

This is a multicenter, double-blind, randomized, parallel-group, Phase III study to compare the efficacy and safety of Hercules plus docetaxel or paclitaxel (i.e., taxane) versus Herceptin® plus taxane in patients with HER2+ MBC with continuation of single agent Hercules versus Herceptin® for patients who have at least stable disease (SD) in order to evaluate continued safety and immunogenicity.

Eligible patients will be centrally randomized in a 1:1 fashion to receive either Hercules in combination with taxane or Herceptin® in combination with taxane. Patients will be stratified by:

- Tumor progression into metastatic phase ≥2 years OR <2 years after primary diagnosis (calculated as time from primary tumor surgery until randomization). Patients diagnosed with primary metastatic disease will be classified together with the patients who progressed <2 years, regardless of the date of tumor surgery.
- Estrogen receptor (ER)/progesterone receptor (PgR) status (ER and/or PgR positive/ER and PgR negative).
- Type of taxane received (e.g., paclitaxel or docetaxel). Investigator decision at the site level prior to the start of screening.

The study will consist of 2 parts.

In Part 1, Hercules plus taxane or Herceptin® plus taxane will be administered for a minimum of 8 treatment cycles (1 treatment cycle = 3 weeks based on trastuzumab administration) unless the patient experiences unacceptable side effects, disease progression or is prematurely withdrawn from treatment (see Section 9.1). Patients will be monitored for response to therapy (SD, partial response [PR] or complete response [CR]).

1. Those with at least SD will proceed to Part 2 of the study, where single agent Herceptin® or Hercules is administered.

2. Those with SD can continue combination of trastuzumab and the taxane therapy beyond 24 weeks at the Investigator’s discretion in Part 1 or stop the taxane and continue to Part 2 of the study.

3. Those who are intolerant to therapy during Part 1 or who have responded to therapy and decline participation in Part 2 of the study will be discontinued from the study, treated at the Investigator’s discretion and followed for long term survival.

4. Those who have progressed during Part 1 will be discontinued from the study and will be followed for long term survival.
Trough (C_{\text{min}}) blood samples (pre-infusion) will be collected for trastuzumab PK analysis for all patients in Part 1 of the study. Summary statistics of observed trough concentrations (C_{\text{min}}) will be presented for all patients by treatment group. It is not intended that the study is powered for this secondary endpoint to demonstrate bioequivalence in C_{\text{min}}, but similarity of the results will be evaluated.

End of infusion (C_{\text{max}}) samples will be collected from all patients in Cycle 1 and Cycle 6. A population PK subset of patients will provide additional consent and will have additional blood samples collected in the first dosing interval and at approximate steady-state. We anticipate that approximately 80 patients will need to be enrolled in this subset collection in order to obtain sufficient samples for analysis. Concentration and covariate data will be analyzed by PopPK methods for all patients with evaluable PK data. Empiric Bayesian estimates of PK model parameters will be obtained for all patients. PK parameters and exposure estimates (AUC, C_{\text{max}}, C_{\text{min}}, clearance(s), volume(s), and half-life) will be compared between the Hercules and Herceptin® treatment arms. For all relevant details concerning the PK assessments, blood sampling, and analyses refer to the Study Manual.

**Exploratory Evaluations:** In addition, during Part 1 of the study, blood samples will be collected in all patients to assess the impact of soluble shed HER2/ECD on PK and efficacy at pre-dose in Cycles 1, 3, 5 and 7, and end of treatment (EOT). Additional samples (ECD) will be obtained in Cycles 9, 13 and every 4 cycles thereafter, EOT and end of study (EOS) for continued evaluation of immunogenicity in patients continuing to receive therapy. A blood sample will be obtained in Cycle 1, on Day 1 for assay development and validation.

In Part 2, all patients who have at least SD will continue with either Hercules alone or Herceptin® alone (i.e., without taxane) until disease progression, unacceptable toxicity or death, whichever occurs first (see 1).

The primary analysis of the best ORR will be performed at Week 24. A formal interim analysis will be overseen by the data and safety monitoring board (DSMB).

Additional safety and efficacy analyses will be performed in Part 2 and will be described in an addendum to the main clinical study report (CSR). Any exploratory analysis performed will also be done at that time.
Figure 3.1 Study Design

Part 1: Combined Treatment/PK analysis

Hercules
- Loading dose 8 mg/kg
- Maintenance dose 6 mg/kg Q3W

Herceptin®
- Loading dose 8 mg/kg
- Maintenance dose 6 mg/kg Q3W

The day after trastuzumab infusion
Docetaxel 75 mg/m² Q3W cycles
or Paclitaxel 80 mg/m² weekly 30 min after trastuzumab infusion

Part 2: Single Treatment

Stable disease after 8 cycles
Hercules Maintenance dose until disease progression
Stable disease can continue with Part 1 beyond Cycle 8*

Stable disease after 8 cycles
Herceptin® Maintenance dose until disease progression

R = Randomization
(within 3 days prior to Cycle 1, Day 1)

* Continue 3 week cycles; if stable disease after 8 cycles, can continue combination treatment on Part 1 at Investigator's discretion

8 Cycles = 24 weeks

Up to 28 days
Cycle 1
Cycles 2 – 8*

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4 SELECTION OF STUDY POPULATION

It is anticipated that up to 600 adult male and female patients with HER2+ MBC will be included in the study. Patients will be screened for eligibility based on the following criteria within 4 weeks prior to study day 1 (Day 1), which is defined as the day of first dosing with Hercules or Herceptin®.

4.1 INCLUSION CRITERIA

Patients must meet the following criteria during the screening examination period to be eligible to participate in this study:

1. ≥18 years of age.
3. Locally recurrent or MBC that is not amenable to curative surgery and/or radiation.
4. Documentation of HER2 gene amplification by fluorescent in situ hybridization (FISH); as defined by a ratio >2.0) or documentation of HER2-overexpression by immunohistochemistry (IHC) (defined as IHC3+, or IHC2+ with FISH confirmation) based on sponsor-identified central laboratory prior to randomization (see Section 7.1.1). Archival tumor tissue samples can be used.
5. Documentation of estrogen receptor/progesterone receptor (ER/PgR) status (positive or negative) based on either a local or central laboratory report must be available before randomization.
6. Pathologically confirmed breast cancer with at least one measurable metastatic target lesion (based on RECIST criteria, Version 1.1). Bone, central nervous system (CNS), and skin lesions, as well as lesions that were irradiated, biopsied or had any form of local intervention or surgical manipulation are only to be assessed as non-target lesions. Baseline imaging studies and submitted for central confirmation of target lesions must have been performed in the 4 weeks preceding randomization.
7. Patients with a history of CNS metastases or cord compression are eligible if they have been successfully treated and are off steroids for at least 4 weeks before first dose of investigational product. Patients with newly detected CNS metastases must be successfully treated (e.g., radiotherapy, stereotactic radiosurgery) before being considered for the trial. Patients with known or suspected brain metastases must undergo a baseline brain computed tomography (CT) or magnetic resonance imaging (MRI).
8. Patients previously treated with trastuzumab or lapatinib in the adjuvant setting are allowed if metastatic disease was diagnosed at least one year after the last dose of treatment.

9. Prior treatment with hormonal agents or bisphosphonates/denosumab is allowed. Bisphosphonates/denosumab can be given simultaneously with study treatment but cannot start after randomization and is considered an indication of progressive disease (PD). Hormonal agents must be discontinued prior to beginning study therapy.


11. Screening laboratory values within the following parameters:
   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ (1500/mm$^3$).
   - Platelet count $\geq 100 \times 10^9/L$ (100,000/mm$^3$).
   - Hemoglobin $\geq 9.0$ g/dL (90 g/L), without a prior transfusion in the last 2 weeks.
   - Serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN).
   - Total bilirubin $\leq 1.0 \times$ ULN ($>1$ ULN if documented Gilbert’s disease).
   - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN.
   - AST and/or ALT $<1.5 \times$ ULN, if alkaline phosphatase $>2.5 \times$ ULN.
   - Alkaline phosphatase $>2.5 \times$ ULN, if bone metastases present and no liver dysfunction present.

12. Left ventricular ejection fraction (LVEF) within institutional range of normal as measured by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO).

13. The patient is willing to comply with the protocol and procedures for the duration of the study, including all scheduled visits and examinations.

14. The patient is either not of childbearing potential or is willing to practice birth control by using two different highly effective methods of contraception, or abstain from sexual intercourse for the duration of the study and follow-up. In particular, patients of childbearing potential must:
   - Female patients are to use a method which results in less than 1% failure rate per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence, or vasectomized partner. Have a negative human chorionic
gonadotropin (hCG) serum pregnancy test at screening and by urinary test on Day 1.

- Male patients without vasectomy are required to use a condom with spermicide and their female partner to use another form of contraception.

15. Written informed consent signed by the patient or her legal representative (if patient is unable to provide) prior to any study-related procedures not standard of care.

### 4.2 EXCLUSION CRITERIA

Patients meeting any of the following criteria will be excluded from the study:

1. Prior systemic therapy in the metastatic disease setting. This includes: chemotherapy, signal transduction inhibitors (e.g., lapatinib), HER2 targeted therapy (e.g., trastuzumab), or other investigational anticancer therapy.

2. Prior treatment with neoadjuvant or adjuvant anthracyclines with a cumulative dose of doxorubicin of >400 mg/m², epirubicin dose >800 mg/m².

3. Participation in the active treatment phase of an investigational drug study ≤28 days prior to randomization.

4. Patients with bone or skin as the only site of disease. Patients with skin lesions measurable by CT scans or MRI as only site of measurable disease are allowed.

5. Surgery or radiotherapy ≤2 weeks preceding Day 1. Target lesions have to be outside the irradiated fields and the patient has fully recovered from surgery or radiotherapy.

6. Presence of unstable angina or a history of CHF according to the New York Heart Association criteria, history of myocardial infarction <1 year from randomization, clinically significant valvular disease, serious cardiac arrhythmia requiring treatment, uncontrolled hypertension or known pulmonary hypertension.

7. Peripheral sensory or motor neuropathy Grade 2 or higher according to the National Cancer Institute-Common Terminology Criteria (NCI-CTC) Version 4.03 [19].

8. Any other cancer, including contralateral breast cancer, within 5 years prior to screening with the exception of adequately treated ductal carcinoma in situ, adequately treated cervical carcinoma in situ, or adequately treated basal or squamous cell carcinoma of the skin.

9. Immunocompromized patients, including known seropositivity for human immunodeficiency virus, or current or chronic hepatitis B and/or hepatitis C
infection (as detected by positive testing for hepatitis B surface antigen or antibody to hepatitis C virus with confirmatory testing).

10. Patients with documented severe hypersensitivity reaction to trastuzumab, paclitaxel, docetaxel or excipients used in their formulations, including murine protein remnants and patients with heredity fructose intolerance.

11. Evidence of significant medical illness or abnormal laboratory finding (including dyspnea at rest or serious pulmonary illness) that, in the Investigator’s judgment, will substantially increase the risk associated with the patient’s participation in, and completion of, the study, or could preclude the evaluation of the patient’s response.

5 STUDY TREATMENTS

The term study treatment in this protocol refers to IMPs.

Investigational Medicinal Products

Hercules is investigated to demonstrate biosimilarity to its reference trastuzumab product Herceptin®. For Hercules, please refer to the Investigator’s Brochure (IB) for details.

Herceptin® (trastuzumab; Roche) is a humanized IgG1 monoclonal antibody against HER2. For Herceptin® product information please refer to the SmPC for details (provided in the Pharmacy Manual).

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. Please refer to the paclitaxel SmPC for further details (provided in the Pharmacy Manual).

Docetaxel works in 3 distinct pathways that contribute, directly or indirectly, to apoptosis, or programmed cell death. The main mode of therapeutic action of docetaxel is the suppression of microtubule dynamics (assembly and disassembly). Other modes include disruption of the cell cycle and phosphorylation of Bcl-2. Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells [20]. Please refer to the docetaxel SmPC for further details (provided in the Pharmacy Manual) [31].
Premedication according to local standard of care prior to the administration of either taxane, to reduce the incidence and severity of taxane-related fluid retention as well as the severity of hypersensitivity reactions, should be performed according to the local standard of care unless contraindicated. Please refer to the either docetaxel or paclitaxel SmPCs for further details (provided in the Pharmacy Manual) [31].

5.1 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Patients will be randomized in a 1:1 proportion to Hercules plus taxane (docetaxel or paclitaxel) or Herceptin® plus taxane within 3 days prior to Cycle 1, Day 1. Choice of taxane will be made by the Investigator at each study site and will apply to all patients enrolled by that site prior to the start of screening. A centralized randomization procedure will be used. The Investigator will be authorized to randomize the patients via interactive voice/web response system (IVRS/IWRS) upon review and approval of eligibility criteria by the study Medical Monitor.

Patients will be stratified at randomization based on the following baseline covariates:

- Tumor progression into metastatic phase ≥ 2 years OR < 2 years after primary diagnosis (calculated as time from primary tumor surgery until randomization). Patients diagnosed with primary metastatic disease will be classified together with the patients who progressed < 2 years, regardless of the date of tumor surgery.
- ER/PgR status (ER and/or PgR positive/ER and PgR negative).
- Type of taxane received (e.g., paclitaxel or docetaxel). Investigator decision at the site level prior to the start of screening.

5.2 BLINDING TREATMENT ASSIGNMENT

An unblinded pharmacist will be identified at each center, whose role will be limited to handling the study treatment. Treatment allocation via the IVRS/IWRS system will be provided only to the unblinded pharmacist/designee; and will be sent to the pre-specified fax/email accessible only to unblinded team members.

The unblinded pharmacist will prepare infusion bags of Hercules and Herceptin® and provide them to the Investigator in a blinded manner. Treatment assignment must NOT be disclosed to the Investigator, site or study personnel, or any Sponsor Representative except for the designated site monitor responsible for unblinded monitoring.

The assessors, i.e., the Investigators and site personnel assessing safety and efficacy, the study patients as well as both the local and central radiologists must remain blinded throughout the study (Part 1 and Part 2).

5.2.1 Breaking the blind

Emergency unblinding for an individual patient is not likely to be necessary in this study, even in the presence of serious adverse events (SAEs). However, should the Investigator...
consider this necessary, Investigator will be enabled to unblind the treatment via the IVRS or IWRS, or request the treatment assignment from the unblinded pharmacist. In case of unblinding (intentional or accidental), the Medical Monitor must immediately be notified in writing.

5.3 TREATMENTS ADMINISTERED

The study treatment may only be administered by experienced and trained study team personnel. The dose calculated by the trained study team member(s) must be documented in the source document (e.g., medical record) before the administration of treatment. Facilities and equipment for resuscitation must be immediately available: antihistamines, corticosteroids, and epinephrine.

The Mosteller formula \[21\] equation can be used to calculate the patient’s body surface area (BSA) where BSA is in \(\text{m}^2\), \(W\) is weight in kg, and \(H\) is height in cm (do not modify the dose if the change in weight is <10% from the prior calculation):

\[
BSA = \sqrt{W \times H / 60}
\]

or

\[
BSA = \sqrt{W \times H / 6}
\]

if height is in m:

**Part 1:** In Part 1 of the study, Hercules plus taxane or Herceptin\(^\oplus\) plus taxane will be administered for a minimum of 8 treatment cycles (1 treatment cycle = 3 weeks based on trastuzumab administration) unless the patient experiences unacceptable side effects, disease progression or is prematurely withdrawn from treatment (see Section 9.1). Tumor assessments are to be conducted every 6 weeks (± 3 days) independent of delays in taxane administration. The choice of which taxane is to be administered to all patients enrolled by the site will be determined for each study site by the Investigator prior to the start of screening.

**Trastuzumab**

Trastuzumab (Hercules or Herceptin\(^\oplus\)) will be prepared and administered in accordance with the European SmPC of Herceptin\(^\oplus\). A 3-weekly schedule of 6 mg/kg is considered equivalent to a weekly schedule of 2 mg/kg, as evidenced by PK studies using trastuzumab, in which patients with HER2+ MBC were treated with paclitaxel (175 mg/m\(^2\) every 3 weeks for 6 cycles) [22] combined with trastuzumab (8 mg/kg over 90 min followed by 6 mg/kg over 30 min every 3 weeks for up to 12 months). A weekly schedule of paclitaxel at 80 mg/m\(^2\) has been selected for use in this study.

- The dosing schedule for this study will be 8 mg/kg loading dose on Cycle 1 Day 1, by continuous I.V. infusion over 90 min (± 10 minutes).
- On Cycle 2, Day 1, and on Day 1 of every cycle thereafter, (i.e., beginning 3 weeks after the loading dose) the maintenance dose will be 6 mg/kg
trastuzumab by continuous I.V. infusion over 30 min (± 10 minutes) every 3 weeks throughout the study.

- The reconstituted solution should be added to an infusion bag containing 250 mL of 0.9% sodium chloride solution. Glucose-containing solutions should not be used with this treatment.
- If the patient misses a dose of study treatment by more than 1 week, a re-loading dose of 8 mg/kg of Hercules or Herceptin® should be given over 90 min (± 10 minutes). Subsequent maintenance doses of 6 mg/kg trastuzumab every 3 weeks should be given from that time point forward, according to the protocol.
  - Do Not resume with a re-loading dose of 8 mg/kg if cardiotoxicity was the reason for Hercules or Herceptin® dose delay of more than 1 week, if cardiotoxicity was cause for delay resume with the maintenance dose of 6 mg/kg.

**Taxane Premedication**

All patients should be pre-medicated prior to taxane administration according to the local standard of care (Refer to appropriate SmPC for guidance) in order to prevent severe hypersensitivity reactions.

**Docetaxel**

Docetaxel will be prepared and administered in accordance with the SmPC for the relevant registered product. Docetaxel has been used in different clinical trials as well as in clinical practice in a dose range of 30 - 100 mg/m². Also, the choice of dose of docetaxel has been based on published literature that suggests that a large proportion of studies and Investigators favor dosing patients with docetaxel at 75 mg/m² [23].

- Docetaxel 75 mg/m² of BSA will be administered I.V. over 1-hour (± 10 minutes) Day 1 of a 3 week cycle, for at least 8 cycles, **except for Cycle 1 when docetaxel will be administered on Day 2 of the cycle.**
- Beginning with Cycle 2, Day 1 and every cycle thereafter docetaxel may be given 30 minutes (± 10 minutes) after the Hercules or Herceptin® infusion is completed on Day 1 of the cycle.

**Paclitaxel**

A Phase III study comparing weekly paclitaxel to every 3 week paclitaxel has demonstrated an improvement in response rate and TTP of weekly administration over of the standard paclitaxel schedule [22]. A weekly schedule of paclitaxel at 80 mg/m² has been selected for use in this study.

Paclitaxel will be prepared and administered in accordance with the SmPC for the relevant registered product.
- Paclitaxel 80 mg/m² will be administered weekly over 1 hour (± 10 minutes) except for Week 1 when paclitaxel will be administered 24 hours after the Hercules or Herceptin® administration is completed.
- All of the subsequent administrations of paclitaxel may be given 30 minutes (± 10 minutes) after Hercules or Herceptin® administration is completed.
- At the discretion of the Investigator 1 administration of paclitaxel may be omitted every 4 weeks.

**Part 2:** In Part 2 of the study, all patients who have at least stable disease to the first line combination therapy will continue with the trastuzumab product (i.e., single agent Hercules or Herceptin®) that they were originally allocated to until disease progression, discontinuation, or death. Tumor assessments are to be conducted every 12 weeks (± 3 days) independent of delays in Hercules/Herceptin® administration.

Patients who have progressed will come off study and be treated at the Investigator’s discretion.

### 5.4 DISPENSING AND STORAGE

For docetaxel, paclitaxel, and Herceptin®, please refer to the most current SmPCs for details).

For Hercules, please refer to the IB for details.

### 5.5 DOSE MODIFICATION

#### 5.5.1 Hercules or Herceptin®:

- Infusion (Immunogenicity) Reactions:
  - Decrease the rate of infusion for mild infusion reactions. Localized cutaneous reaction examples include pruritus, flushing, rash.
  - Interrupt the infusion in patients with moderate or severe symptoms, such as flushing, generalized rash, dyspnea, or hypotension (systolic blood pressure (BP) ≤ 100 mmHg moderate and ≤ 80 mmHg severe). Treat as per suggested guidelines in Table 5-3.
  - Collect an ad hoc immunogenicity and PK blood sample (See Part 1 and Part 2 Schedule of Assessments Table 1 and Table 2).

- Cardiac Dysfunction as measured by LVEF (also consult with Medical Monitor):
  - Withhold for at least 4 weeks for:
    - A 16% absolute decrease in LVEF from pre-treatment levels.
    - An LVEF below institutional level normal (ILN) and a 10% absolute decrease in LVEF.
- Repeat LVEF at least every 3 weeks. Permanently discontinue if further decline or no improvement in 9 weeks.

  o Discontinue for:
    - Symptomatic cardiac failure; or
    - Symptomatic decrease of LVEF below ILN; or
    - Symptomatic absolute LVEF decrease of >10% lasting more than 8 weeks; or
    - Suspension of Herceptin® for more than three episodes of cardiomyopathy.

  o Resume treatment with Hercules or Herceptin® at 6 mg/kg if the LVEF returns to normal within 4 - 8 weeks and the Investigator deems the patient medically stable.

  o A consultation with a cardiologist is encouraged if there are any concerns.

5.5.2 Docetaxel:

- Only one docetaxel dose reduction to 60 mg/m² is allowed. Dose reduction below 60 mg/m² is not allowed in this protocol.
- A dose that has been reduced for toxicity must not be re-escalated or re-initiated.
- Patients should discontinue docetaxel should they experience a second episode of severe toxicity.
- Patients who experience severe hypersensitivity reactions should not be re-challenged.
- Patients who discontinue docetaxel due to unacceptable toxicity may either continue to receive Hercules or Herceptin® as a single agent in Part 1 of the study after recovery to Grade 1 or 2 or may be removed from study treatment at the Investigator’s discretion.

5.5.3 Paclitaxel:

- Only one dose reduction of paclitaxel to 70 mg/m² is allowed. Dose reduction below 70 mg/m² is not allowed in this protocol. A dose that has been reduced for toxicity must not be re-escalated or re-initiated and patients should discontinue paclitaxel should they experience a second episode of severe toxicity.
- Patients who discontinue paclitaxel due to unacceptable toxicity may either continue to receive Hercules or Herceptin® as a single agent in Part 1 of the study after recovery to Grade 1 or 2 or may be removed from study treatment at the Investigator’s discretion.
5.5.4  **Dose modification for taxane-related toxicity (paclitaxel or docetaxel):**

- Local laboratory reports will be utilized for dosing and dose adjustment purposes by the Investigator. **It is the Investigators responsibility to have local laboratory analysis performed and results available for review prior to dosing.**

Modification for taxane-related toxicity should be performed according to the following criteria:

- Paclitaxel should be withheld if platelet count is <100,000/mm³. Paclitaxel treatment can be re-instituted when the platelet count recovers to ≥ 100,000/mm³.

- Grade 1 or 2 (NCI-CTC AE Version 4.03 [19]) should not lead to dose modifications without prior consultation with the Medical Monitor.

- Grade 3 (except alopecia): Docetaxel or paclitaxel should be withheld for a maximum of 2 weeks until resolution to ≤ Grade 1, then reinstituted at the next planned cycle, if medically appropriate; Hercules or Herceptin® should be continued.

- Grade 4 toxicities (except anemia) dosing for paclitaxel or docetaxel:
  - Consider discontinuation of taxane or discontinuation from study based on clinical judgment
  - OR
  - Delay until recovery to Grade ≤ 2. Subsequent doses would be reduced by one step for subsequent cycles. Dose once reduced will not be increased.
  - If toxicity does not recover to ≤ Grade 2 within 6 weeks, discontinue taxane or discontinue patient from study.
  - For recurrent Grade 4 or severe toxicities, consult the Medical Monitor prior to continuation.

- Patients who discontinue docetaxel or paclitaxel due to unacceptable toxicity may either continue to receive Hercules or Herceptin® as a single agent in Part 1 of the study or may be removed from study treatment at the Investigator’s discretion after discussion with the Medical Monitor.

In addition, modification should be performed according to the specific scenarios e.g., liver function test, neutropenia etc., described below.
Liver Function Tests

Table 5-1 Taxane Dose Modifications based on Liver Function Tests

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>Transaminases</th>
<th>Alkaline Phosphatase¹</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5 x ULN</td>
<td>Or &lt;2.5 x ULN</td>
<td></td>
<td>75 mg/m² (Full dose) 80 mg/m² (Full dose)</td>
</tr>
<tr>
<td>&gt;2.5 and &lt;3.5 x ULN</td>
<td></td>
<td></td>
<td>Reduce to 60 mg/m² Reduce to 70 mg/m²</td>
</tr>
<tr>
<td>&gt;1.5 x ULN</td>
<td>And &gt;2.5 x ULN</td>
<td></td>
<td>Discontinue taxane. May resume treatment with Hercules or Herceptin® as a single agent in Part 1 of the study, or discontinue from study after discussion with Medical Monitor, at Investigator’s discretion</td>
</tr>
<tr>
<td>&gt;1.0 x ULN</td>
<td>And Any</td>
<td>And Any</td>
<td>Discontinue taxane. May resume treatment with Hercules or Herceptin® as a single agent in Part 1 of the study, or discontinue from study after discussion with Medical Monitor, at Investigator’s discretion</td>
</tr>
</tbody>
</table>

LFT = liver function test; ULN = upper limit of normal
Local lab results on Day 1 of the respective treatment cycle should be used as the basis for taxane dose modifications.
*Assume dose adjustments with baseline LFTs normal at randomization.
¹ If bone metastases present at baseline, alkaline phosphatase can be >2.5 x ULN, but an elevation during treatment has to be evaluated in the clinical context and consult with the Medical Monitor.

In case of history of Gilbert syndrome, dose modifications for bilirubin do not apply.
- In case of liver metastasis, taxane dose reductions should not be performed if there are no liver function abnormalities as noted above, but the taxane should be discontinued if the criteria for dose discontinuation have been met.
- Patients who discontinue docetaxel or paclitaxel due to unacceptable toxicity may either continue to receive Hercules or Herceptin® as a single agent in Part 1 of the study, or may be removed from study treatment at the Investigator’s discretion.

Neutropenia

Severe neutropenia is defined as:
- Neutrophils <0.5 x 10⁹/L for longer than 3 days.
- Neutrophils <1.0 x 10⁹/L for longer than 7 days.

Febrile neutropenia is defined as:
- Neutrophils <1.0 x 10⁹/L with a single recorded temperature of >38.3°C; or
- Sustained temperature of ≥38°C for more than 1 hour.
Beware that in case of severe neutropenia despite the presence of infection the patient may not be febrile.

### Table 5-2 Taxane Dose Modifications based on Neutropenia

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Action recommended for subsequent cycles</th>
</tr>
</thead>
</table>
| Severe neutropenia (Grade 3 - 4) Febrile neutropenia | • The first episode: Consider granulocyte colony stimulating factor (G-CSF) according to the manufacturer's recommendations and antibiotic prophylaxis (e.g., ciprofloxacin 500 mg twice daily Days 5 - 14) for the remaining cycles.  
• If there is a second episode while receiving prophylaxis: Reduce the dose of taxane during the subsequent cycles or discontinue taxane and after recovery of neutrophils >1.5 x 10^9/L; continue treatment with single agent Hercules or Herceptin® in Part 1 of the study or discontinue patient from study as per Investigator's discretion. |

### Blood Counts on Day 1 of Cycles 2 - 8

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Action to be taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.5</td>
<td>Treat on time</td>
</tr>
</tbody>
</table>
| <1.5                   | • Start G-CSF according to manufacturer's recommendations. Complete blood count should be repeated approximately every other day till Day 35 of the treatment cycle. Proceed with full dose taxane as soon as absolute neutrophil count (ANC) ≥1.5 x 10^9/L (after administration of the next dose of investigational medicinal product).  
• If there is no recovery by Day 35 (ANC <1.5 x 10^9/L), discontinue patient from study.  
• If there is a second episode of prolonged recovery, reduce the dose of taxane during the subsequent cycles. |

### Hypersensitivity Reactions

If a reaction occurs, the specific treatment that is medically indicated for a given symptom will be instituted (e.g., epinephrine in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.). In addition, it is recommended to take the measures listed below:
<table>
<thead>
<tr>
<th><strong>Table 5-3  Dose Modification based on Infusion Reactions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild symptoms:</strong> Localized cutaneous reaction such as: pruritus, flushing, rash</td>
</tr>
<tr>
<td>• Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside.</td>
</tr>
<tr>
<td>• Then complete the infusion at the initially planned rate.</td>
</tr>
<tr>
<td><strong>Moderate symptoms:</strong> Any symptom not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure (BP) ( \leq 100 ) mmHg</td>
</tr>
<tr>
<td>• Stop the infusion.</td>
</tr>
<tr>
<td>• Consider intravenous (I.V.) dexamethasone 10 mg (or equivalent) and I.V. diphenhydramine 50 mg (or equivalent).</td>
</tr>
<tr>
<td>• Resume the infusion after subsiding of symptoms at the same rate or decrease in rate.</td>
</tr>
<tr>
<td>• At subsequent cycles consider I.V. dexamethasone 10 mg (or equivalent) and I.V. diphenhydramine 50 mg (or equivalent) 1 hour before infusion, in addition to the premedication planned.</td>
</tr>
<tr>
<td><strong>Severe symptoms:</strong> Such as bronchospasm, generalized urticaria, hypotension with systolic BP ( \leq 80 ) mmHg, angioedema</td>
</tr>
<tr>
<td>• Stop the infusion.</td>
</tr>
<tr>
<td>• Give I.V. dexamethasone 10 mg (or equivalent) and I.V. diphenhydramine 50 mg (or equivalent), add epinephrine as needed.</td>
</tr>
<tr>
<td>• Whenever possible resume the infusion within 3 hours after recovery or re-infuse the patient within 72 hours using I.V. dexamethasone 20 mg (or equivalent) and I.V. diphenhydramine 50 mg (or equivalent) 1 hour prior to resumption of infusion.</td>
</tr>
<tr>
<td>• At the subsequent cycle give dexamethasone (or equivalent) 20 mg orally the evening before chemotherapy, the morning of chemotherapy, and 1 hour before taxane infusion. Additionally diphenhydramine (or equivalent) at 50 mg I.V. 1 hour before taxane infusion.</td>
</tr>
<tr>
<td>• If a severe reaction recurs, patient should discontinue the treatment related with the reaction. Patients may either continue to receive Hercules or Herceptin® or taxane as a single agent in Part 1 of the study or be discontinued from study at the Investigator’s discretion. Events should be recorded as a serious adverse event (SAE) and reported to the sponsor within 24 hours.</td>
</tr>
<tr>
<td><strong>Anaphylaxis (NCI-CTC AE Version 4.03 Grade 4 reaction to trastuzumab infusion reaction) [19]</strong></td>
</tr>
<tr>
<td>• Report as SAE.</td>
</tr>
<tr>
<td>• Take a blood sample for anti-drug antibodies formation detection and PK.</td>
</tr>
<tr>
<td>• Discontinue treatment related with reaction. Patients may either continue to receive Hercules or Herceptin® or taxane as a single agent in Part 1 of the study or be discontinued from study at the Investigator’s discretion.</td>
</tr>
</tbody>
</table>

**Fluid Retention (peripheral edemas and/or effusions)**

The clinical tolerance of the patient and the medical judgment of the Investigator will determine if it is in the patient's best interest to continue or to discontinue the taxane. It is recommended, however, that patients with fluid retention of Grade 3 severity should have the taxane withdrawn; patients may either continue to receive Hercules or Herceptin® as a single agent in Part 1 of the study or be discontinued from the study at the Investigator’s discretion.
Nail Changes

If nail changes of Grade ≥2 occur the patient should consult a dermatologist or a person trained in nail care.

5.6 ELIGIBILITY FOR PART 2 OF PROTOCOL

Patients with documented CR, PR based upon local radiographic tumor assessments and clinical evaluation as per RECIST 1.1, will discontinue docetaxel or paclitaxel after a minimum of 8 completed taxane cycles. Patients will then enter Part 2 after Cycle 9 assessments are completed. Tumor assessments are to be conducted every 12 weeks (± 3 days) independent of delays in treatment administration.

Patients with SD are eligible for Part 2 of the protocol or can continue at the Investigator’s discretion to receive treatment in Part 1 until locally documented tumor response, unacceptable toxicity, disease progression or is prematurely withdrawn from treatment (see Section 9.1).

5.7 TREATMENT AFTER END OF STUDY TREATMENT

After the end of the study treatment, each patient should be treated according to standard clinical practice. Standard treatment should be initiated as appropriate upon completion of the EOS Visit.

5.8 DRUG ACCOUNTABILITY AND TREATMENT COMPLIANCE

The pharmacist (or authorized designee) is responsible for maintaining accurate records of the receipt and administration of all study treatment supplies during the course of the study and recorded in both the electronic case report form (eCRF) and the appropriate study drug accountability log by patient. The unblinded study monitor will periodically monitor compliance by inspecting the source documents, study treatment accountability, inventory, and storage.

Handling and accountability of Hercules and Herceptin® will be performed only by the unblinded pharmacist, or designee and the authorized unblinded study monitor.

Chain or custody of the study drug will be followed in accordance with the individual site’s standard procedures, which will be documented by the site.

Patients who miss two consecutive treatment cycle visits will be considered non-compliant and will be withdrawn from the study (Section 9.1 Patient Withdrawal).

5.9 FINAL RECONCILIATION AND DESTRUCTION

All used and unused vials of Hercules, Herceptin®, docetaxel and paclitaxel must be accounted for; at the end of the study a final reconciliation will be performed and captured in the Site Inventory Form.
After finalization of reconciliation via review by the authorized unblinded study monitor, taxanes will be destroyed locally following individual site’s standard procedures verified by the study monitor. All other IMPs will either be destroyed locally or returned to designated vendor for destruction per the Pharmacy Manual. All documentation must be retained by the site in the site files.

5.10 LABELING, FORMULATION AND PACKAGING

Study treatment labels (for Hercules and Herceptin®, docetaxel and paclitaxel) will comply with the EU guidelines to GMP “Medicinal Products for Human and Veterinary Use; Annex 13: Investigational medicinal products” and the legal requirements of each country, and will be printed in local languages. The flag label of the study treatment administered will be retained and attached to the Drug Accountability Form.

6 CONCOMITANT MEDICATIONS AND THERAPIES

All prior medications (i.e., given 3 weeks prior to the screening visit) and concomitant medications until EOT/EOS visit (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF. The indication, dose, duration, and changes thereof will be recorded.

The dose and duration of all pharmacological therapy for breast cancer (trastuzumab, chemotherapy or other e.g., biological, endocrine) at any time until EOS visit will be recorded.

The dose, duration, and type of any radiological therapy for breast cancer at any time until EOT/EOS visit will be recorded.

6.1 PERMITTED

The following therapies are permitted during the study:

- **Glucocorticosteroids:** All patients should receive premedication according to the local standard of care prior to the administration of docetaxel or paclitaxel, to reduce the incidence and severity of taxane-related fluid retention as well as the severity of hypersensitivity reactions. Bisphosphonates or other bone-directed therapy e.g., denosumab: All patients with symptomatic bone disease should be offered treatment based on standard national guidelines. If a patient has not yet initiated treatment it must be initiated before randomization.

- **Concomitant endocrine treatment for breast cancer is allowed in Part 2 of the study only.**

- **Granulocyte Colony Stimulating Factor prophylaxis is allowed for febrile neutropenia, clinical infection or prolonged neutropenia in previous cycles according to current European Organization for Research and Treatment of Cancer (EORTC) or American Society of Clinical Oncology guideline, as updated during the study [24, 25].**
• Any other therapy deemed necessary by the Investigator is allowed, except the therapies identified as prohibited in Section 6.2.

6.2 PROHIBITED

The following concomitant therapies are prohibited:

• Immunotherapy: Concomitant immunotherapy for the treatment of breast cancer will not be permitted.

• Any tumor-directed therapy from study screening until the completion of study treatment. Directed radiotherapy to bony metastatic lesion(s) may be allowed at the discretion of the Study Sponsor.

• The use of any other IMP or experimental procedure.

• Non-study drug therapy for MBC: The introduction of other treatment indicated for use in MBC during the study will be considered as study treatment failure and the patient will be discontinued from study treatment, with the exception of hormonal therapy which is permitted in Part 2 of the study for ER/PgR positive patients, as noted above.

• Docetaxel: *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolized by (and thus may inhibit the enzyme competitively) cytochrome P450-3A (CYP450-3A) such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. As a result, caution should be exercised when treating patients with these medicinal products as concomitant therapy since there is a potential for a significant interaction.

• Paclitaxel: Caution should be exercised during concurrent administration of active substances which are metabolized in the liver as such active substances may inhibit the metabolism of paclitaxel. The metabolism of paclitaxel is catalyzed, in part, by CYP450 isoenzymes, CYP2C8, and 3A4. Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel (to 6α-hydroxypaclitaxel) is the major metabolic pathway in humans. Based on current knowledge, clinically relevant interactions between paclitaxel and other CYP2C8 substrates are not anticipated. Concurrent administration of ketoconazole (a known potent inhibitor of CYP3A4) does not inhibit the elimination of paclitaxel in patients; thus, both medicinal products may be administered together without dosage adjustment. Further data on the potential of interactions between paclitaxel and other CYP3A4 substrates/inhibitors are limited. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g., erythromycin, fluoxetine, gemfibrozil) or induce (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or 3A4.
7 STUDY PROCEDURES

Patients will provide a written informed consent before any study related procedure is initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Activities (Table 1 and Table 2). Throughout the study, every reasonable effort should be made to follow the timing of assessments and procedures in the schedule of events for each patient. Deviations from the schedule should be avoided, but a ± 3 day visit window for cycle visits is allowed. Study treatment cycles should be scheduled with respect to the previous cycle. Tumor assessments are to be conducted every 6 weeks (± 3 days) up to Cycle 8, independent of delays in treatment administration and every 12 weeks (± 3 days) independent of delays in treatment administration Cycle 9 and beyond.

The following procedures will be performed before dosing with the study treatment at visits at which it is indicated as required: imaging for tumor assessment, blood sampling for routine hematology and blood chemistry, ECD, and immunogenicity, urinalysis (including pregnancy testing), electrocardiogram (ECG), assessment of LVEF, ECOG performance status (ECOG PS), physical examination, and measurement of the patient’s weight and height (in order to calculate the correct dose of study treatment).

The following procedures are performed locally throughout the study - imaging hematology, chemistry, coagulation, urinalysis and pregnancy testing. Please note, imaging is sent centrally for review and at baseline confirmation of measurable disease is required prior to randomization.

The following procedures are performed centrally throughout the study - HER-2, ER/PgR, PK, ECD, immunogenicity, exploratory analysis, and ECG.

Details of adverse events (AEs) and concomitant medications and procedures will be recorded on a continuous basis throughout the study until the EOT evaluation.

7.1 STUDY PERIODS AND VISITS

7.1.1 Screening

The patient must be screened within 28 days prior to randomization. The following procedures will be performed at screening:

- Written informed consent obtained.
- Collection of demographic information.
- Recording of medical history, including disease history and current therapies (e.g., prescription and non-prescription medications).
- Confirmation of HER2 overexpression will be done by the sponsor approved central laboratory for randomization. As IHC or FISH may not be feasible on the primary
tumor sample due to variability of locally used fixation and embedding procedures, sampling of metastatic tissue is strongly encouraged whenever possible. A positive result on either the primary breast tumor or metastasis is required for confirmation of eligibility and randomization. In case of contradictory results from the assessment of the primary tumor and metastasis, the patient has to be positive based on the assessment of the metastasis. For all the patients, IHC will be performed firstly. To be eligible for the study, patients have to be IHC3+. If a patient is IHC2+, then FISH will be done, and the patient must also be FISH+ (see Section 7.3.4 Overexpression of HER2).

- Documentation of ER/PgR status (positive or negative) based on either a local or central laboratory report must be available before randomization.
- An ECG will be recorded. LVEF will be determined by gated MUGA or ECHO.
- ECOG PS will be evaluated and recorded.
- Tumor burden will be assessed using RECIST criteria version 1.1 (see Appendix A). A CT or MRI scan of the chest and upper abdomen, bone scan and confirmatory x-rays of lesions on bone scan consistent with metastatic disease. If clinically indicated CT or MRI scan of the brain will be performed to quantify the disease burden within 28 days of Cycle 1, Day 1. Contact the Medical Monitor if the baseline bone scan has been performed outside the 28 day screening window. Bone scan must be repeated if performed beyond 42 days prior to projected Cycle 1, Day 1 visit.

- Physical examination will be performed, including weight and vital signs.
- A blood sample will be taken for hematology, serum chemistry, coagulation, and serum pregnancy testing for women of childbearing potential. A urine sample for dipstick urinalysis will be performed.
- Any SAEs reported by the patient after the Informed Consent Form (ICF) is signed will be recorded.

Procedures for rescreening patients who initially fail the study entry criteria are described in Section 13.3 Screening Failures.

7.1.2 Randomization

Patients who after the screening assessments meet all of the inclusion and none of exclusion criteria are considered eligible for entry into the study and will be randomized into the study within 3 days prior to Day 1. The randomization procedures are described in Section 5.1.
7.1.3 Treatment period

7.1.3.1 Study Part 1 with taxane

Patients will be treated with Hercules plus taxane or Herceptin® plus taxane for at least 8 treatment cycles (1 treatment cycle = 3 weeks based on trastuzumab administration) until disease progression, unacceptable toxicity or discontinuation (see Section 9.1). Tumor assessments are to be conducted every 6 weeks (± 3 days) independent of delays in treatment administration up to Cycle 8 and every 12 weeks (± 3 days) Cycle 9 and beyond regardless of treatment administration. Premedication prior to the administration of the taxane will be performed according to the local standard of care (see Section 5.3 for Treatment Administration information and appropriate SmPC for guidance).

Cycle 1

On Day 1 of Cycle 1, the following procedures will be carried out prior to dosing:

- A physical examination including vital signs will be carried out and the patient’s weight and height recorded in order to calculate the correct dose of study treatment.

- Blood sampling for immunogenicity, hematology, serum chemistry, coagulation, exploratory analyses, and ECD analysis will be carried out. Urine dipstick for urinalysis will be performed. All patients of child bearing potential will also be required to have a urine pregnancy test.

- PK blood samples for $C_{\text{min}}$ will be taken before Hercules/Herceptin® infusion from all patients and a $C_{\text{max}}$ sample will be taken from all patients immediately post infusion. A different I.V. line must be used. (Refer to the Study Manual for PK sampling details).

- After the pre-dose procedures described above have been performed, patients will be dosed with their allocated treatment - either Hercules or Herceptin® (see Section 5.3).

- AEs, concomitant medications and procedures will be recorded.

- Premedication will be performed according to the local standard of care for taxane administration. Premedication administration (Refer to appropriate SmPC for guidance) should begin after the patient has been dosed with their randomized treatment of either Hercules or Herceptin® on Day 1.

On Day 2 of Cycle 1, the following procedures will be carried out in the following sequence:

- For patients in the PopPK subset, a blood sample for PopPK analysis will be taken before administration of docetaxel or paclitaxel. (Refer to the Study Manual for PK sampling details).

- Premedication for taxane administration will be performed according to the local standard of care.
- Dosing with taxane (see Section 5.3).
- AEs, concomitant medications and procedures will be recorded.

On **Day 8** of Cycle 1, the following procedures will be carried out:
- A blood sample will be taken for hematology, coagulation, serum chemistry.
- A urine sample for dipstick urinalysis will be done.
- AEs, concomitant medications and procedures will be recorded.
- For patients in the PopPK subset, a blood sample will be taken for PopPK (Refer to the Study Manual for PK sampling details).
- Premedication for taxane administration will be performed according to the local standard of care for patients receiving paclitaxel.
- Dosing with taxane (see Section 5.3) for patients receiving paclitaxel.

On **Day 15** of Cycle 1, the following procedures will be carried out:
- Premedication for taxane administration will be performed according to the local standard of care for patients receiving paclitaxel.
- Dosing with taxane (see Section 5.3) for patients receiving paclitaxel.

**Cycles 2 - 8 (at 3-weekly intervals, +/- 3 days)**

At each subsequent cycle in Part 1, the following procedures will be carried out prior to dosing:
- Physical examination including vital signs will be carried out and the patient’s weight recorded in order to calculate the correct dose of study treatment.
- ECOG PS will be evaluated and recorded.
- A blood sample will be taken prior to study treatment administration at each cycle for hematology, coagulation, serum chemistry, and urine sample for dipstick urinalysis and pregnancy testing for women of child bearing potential.
- Premedication for taxane administration will be performed according to the local standard of care (Refer to appropriate SmPC for guidance).
- At Cycles 3, 5, and 7 blood samples will be taken for immunogenicity and ECD analysis.
- At Cycles 3, 5, and 7 the tumor burden and response will be evaluated using the same imaging methods as at baseline, i.e., CT or MRI of the chest and upper abdomen, and head CT or MRI for patients with brain involvement and bone scans for patients where clinically indicated. Tumor assessments are to be conducted every 6 weeks (± 3 days) independent of delays in treatment administration.
- At Cycle 5 only an ECG will be recorded, LVEF will be determined by ECHO or MUGA.

- At Cycles 2, 4, 6, and 8 a blood sample for \( C_{\text{min}} \) will be taken before Hercules/Herceptin® infusion from all patients (Refer to the Study Manual for PK sampling details).

- At Cycle 6 only a post infusion blood sample for \( C_{\text{max}} \) will be taken from all patients. A different I.V. line must be used (Refer to the Study Manual for PK sampling details).

- After the pre-dose procedures described above have been performed, patients will be dosed with their randomized treatment of either Hercules or Herceptin®.

- At Cycle 4 for patients in the PopPK subset, a blood sample for PopPK at \( C_{\text{max}} \) will be taken immediately after the completion of infusion. A different I.V. line must be used (Refer to the Study Manual for PK sampling details).

- Once all of the above is completed, Hercules or Herceptin® may be administered. Taxane may be administered 30 minutes after Hercules or Herceptin® administration is completed (see Section 5.3).

- AEs, concomitant medications and procedures will be recorded.

- For patients in the PopPK subset, on any day during Cycles 2 - 8, at any 2 unscheduled visits that the patient attends 2 additional serum samples for PK should be collected. The precise date and time must be recorded (Refer to the Study Manual for PK sampling details).

Cycle 9 Part 1 (+/- 3 days)

Patients with at least SD (documented) will move to Part 2 of the study based upon local radiographic tumor assessments and clinical evaluation.

Patients who have achieved a locally documented SD are eligible for Part 2, but at the Investigator’s discretion can continue to receive treatment on Part 1 until documented response, unacceptable toxicity, disease progression or premature withdrawal from treatment (see Section 9.1).

The Cycle 9 evaluation of the study and will be conducted 3 weeks after Cycle 8, Day 1 in order to keep alignment with the treatment cycles. The following procedures will be carried out prior to dosing:

- Physical examination including vital signs will be carried out and the patient’s weight recorded in order to calculate the correct dose of study treatment.

- ECOG PS will be evaluated and recorded.
The tumor burden and response will be evaluated. Tumor assessments are to be conducted every 12 weeks (± 3 days) independent of delays in treatment administration.

A blood sample will be taken for hematology, coagulations, serum chemistry, immunogenicity, and ECD. A urine sample will also be taken for dipstick urinalysis and pregnancy testing.

An ECG will be recorded and LVEF by ECHO or MUGA will be determined.

AEs, concomitant medications and procedures will be recorded.

Blood sample for C\textsubscript{min} analysis will be taken from all patients (Refer to the Study Manual for PK sampling details).

After the pre-dose procedures described above have been performed, patients continuing on Part 1 of the study will receive premedication according to local standard of care for taxane administration (Refer to appropriate SmPC for guidance) and continue to be dosed with their randomized treatment of either Hercules or Herceptin\textsuperscript{®} and taxane.

Patients who discontinued taxane due to toxicity and after recovery receive Hercules or Herceptin\textsuperscript{®} as a single agent in Part 1 may continue to do so at the Investigator’s discretion, if they are receiving clinical benefit but have not achieved a documented SD. Patients receiving single agent Hercules or Herceptin\textsuperscript{®} in Part 1 will move into Part 2 of the study only after achieving documented SD.

Cycles XS (10 and Beyond at 3-weekly intervals, +/- 3 days) Part 1

At each cycle, the following procedures will be carried out prior to dosing:

- Physical examination including vital signs will be carried out and the patient’s weight recorded in order to calculate the correct dose of study treatment.

- ECOG PS will be evaluated and recorded.

- A blood sample will be taken at each cycle for hematology, coagulation, and serum chemistry; and urine sample for dipstick urinalysis and for pregnancy testing for women of childbearing potential. A blood sample for ECD and immunogenicity will be drawn at Cycle 13 and every 4 cycles thereafter.

- Premedication for taxane administration will be performed according to the local standard of care (Refer to the appropriate SmPC for guidance).

- AEs, concomitant medications and procedures will be recorded.

- At Cycle 13 and every 4 cycles thereafter, the tumor burden and response will be evaluated, using the same imaging methods and settings as at baseline, i.e., CT or MRI of the chest and upper abdomen, and head CT or MRI for patients with brain involvement and bone scans for patients where clinically indicated. Tumor
assessments are to be conducted every 12 weeks (± 3 days) independent of delays in treatment administration.

- An ECG will be recorded at Cycle 13 and every 4 cycles thereafter.
- LVEF by ECHO or MUGA will be determined at Cycle 13 and every 4 cycles thereafter.

After the pre-dose procedures described above have been performed, patients will continue to be dosed with their randomized treatment of either Hercules or Herceptin® and taxane (see Section 5.3).

Patients who discontinued taxane due to toxicity and receive Hercules or Herceptin® as a single agent in Part 1 may continue to do so at the Investigator’s discretion, if they are receiving clinical benefit but have not achieved a CR/PR after 8 cycles of treatment. Patients receiving single agent Hercules or Herceptin® in Part 1 will move into Part 2 of the study only after achieving documented SD.

End of Treatment (for Part 1)

When the patient discontinues treatment, the following assessments should be completed:

- Physical examination including vital signs will be carried out.
- ECOG PS will be evaluated and recorded.
- The tumor burden and response will be evaluated if not performed within the prior 6 weeks (2 cycles).
- A blood sample will be taken for hematology, coagulation, ECD, immunogenicity, and serum chemistry. A urine sample will also be taken for dipstick urinalysis and pregnancy testing.
- LVEF by ECHO or MUGA will be determined if not already obtained within the 6 weeks (2 cycles) prior to EOT.
- AEs, concomitant medications and procedures will be recorded.

End of Study

The EOS visit should be performed 28 days (+/- 7 days) after the last dose of study treatment.

- Physical examination including vital signs will be carried out.
- ECOG PS will be evaluated and recorded.
- A blood sample will be taken for hematology, coagulation, ECD, immunogenicity, and serum chemistry. A urine sample will also be taken for dipstick urinalysis.
- An ECG will be recorded.
• AEs, concomitant medications and procedures will be recorded.

7.1.3.2 Study Part 2 single agent Trastuzumab

At the end of Part 1 patients with response to therapy locally documented SD will continue to receive the originally randomized treatment of either Hercules or Herceptin® as a single agent i.e., without taxane, until disease progression, unacceptable toxicity or premature withdrawal (see Section 9.1). Tumor assessments are to be conducted every 12 weeks (± 3 days) independent of delays in treatment administration.

Cycle 9 (As start of Part 2)

The Cycle 9 evaluation of the study coincides with the first primary efficacy analysis and will be conducted 3 weeks after Cycle 8, Day 1 in order to keep alignment with the treatment cycles. The following procedures will be carried out prior to dosing:

• Physical examination including vital signs will be carried out and the patient’s weight recorded in order to calculate the correct dose of study treatment.
• ECOG PS will be evaluated and recorded.
• The tumor burden and response will be evaluated. Tumor assessments are to be conducted every 12 weeks (± 3 days) independent of delays in treatment administration.
• A blood sample will be taken for hematology, coagulation, ECD, immunogenicity, and serum chemistry. A urine sample will also be taken for dipstick urinalysis and pregnancy testing for women of childbearing potential.
• An ECG will be recorded and LVEF by ECHO or MUGA will be determined.
• A blood sample for $C_{\text{min}}$ will be taken before Hercules/Herceptin® infusion from all patients (Refer to the Study Manual for PK sampling details).
• AEs, concomitant medications and procedures, will be recorded.

After the pre-dose procedures described above have been performed, the patients will be dosed with their randomized treatment of either Hercules or Herceptin® alone (see Section 5.3).

Cycles XR (10 and Beyond at 3-weekly intervals)

At each cycle, the following procedures will be carried out prior to dosing:

• Physical examination including vital signs will be carried out and the patient’s weight recorded in order to calculate the correct dose of study treatment.
• ECOG PS will be evaluated and recorded.
A blood sample will be taken at each cycle for hematology, coagulation, immunogenicity, and serum chemistry and a urine sample will be taken for dipstick urinalysis and pregnancy testing for women of childbearing potential.

AEs, concomitant medications and procedures will be recorded.

At Cycle 13 and every 4 cycles thereafter, the blood sample for ECD and immunogenicity will be taken and the tumor burden and response will be evaluated, using the same imaging methods and settings as at baseline, i.e., CT or MRI of the chest and upper abdomen, and head CT or MRI for patients with brain involvement and bone scans for patients where clinically indicated.

An ECG will be recorded.

LVEF by ECHO or MUGA will be determined.

After the pre-dose procedures described above have been performed, patients will be dosed with their randomized treatment of either Hercules or Herceptin® alone (see Section 5.3).

End of Treatment (for Part 2)

The EOT evaluation for study Part 2 will be performed when the patient has discontinued Hercules/Herceptin® administration.

A physical examination including vital signs will be carried out.

ECOG PS will be evaluated and recorded.

The tumor burden and response will be evaluated if not performed within the prior 6 weeks (2 cycles).

A blood sample will be taken for hematology, coagulation, serum chemistry, ECD, and immunogenicity. A urine sample will also be taken for dipstick urinalysis and pregnancy testing for women of childbearing potential.

LVEF by ECHO or MUGA will be determined.

AEs, concomitant medications and procedures will be recorded.

End of Study

The EOS visit should be performed 28 days (+/- 7 days) after the last dose of study treatment.

Physical examination including vital signs will be carried out.

ECOG PS will be evaluated and recorded.

A blood sample will be taken for hematology, coagulation, ECD, immunogenicity, and serum chemistry. A urine sample will also be taken for dipstick urinalysis.

An ECG will be recorded.
LVEF by ECHO or MUGA will be determined.

AEs, concomitant medications and procedures will be recorded.

7.1.4 Follow-Up of discontinued patients

Documented survival follow-up by phone or in person should be performed every 3 months for up to 36 months or until 240 death events, whichever occurs first, from the date of randomization. In case of death, document date of death and whether the death was due to the primary disease i.e., breast cancer.

Confirm and document in the patient’s medical record the continued use of contraception during the first 2 survival follow-up contacts i.e. 7 months after last dose of blinded trastuzumab.

LVEF by ECHO or MUGA scans to be obtained every 6 months for 24 months from date of EOT Visit. All SAEs will be recorded from the time ICF is signed until the EOS visit, and should be followed until resolution or deemed stable. However, the Investigator should report SAEs to the Sponsor safety contact even beyond this timeframe, when the Investigator becomes aware and the SAE is considered to be reasonably related to the study drug as described in Section 8.2. Site staff will collect information regarding new SAEs or resolution of on-going SAEs, including concomitant medications used to treat any SAE. All other assessments may be performed in accordance with the routine practice.

7.1.5 Unscheduled visits

Assessment during unscheduled visits should be guided by the reason for the visit. Unscheduled visits with all needed assessments are to be performed when there is suspicion of progression of disease. An unscheduled MRI/CT can be performed at any scheduled/unscheduled visit when progression of disease is suspected.

At any 2 unscheduled visits (performed for any reason) that the patient attends during cycles 2 - 8, two random samples for PopPK should be taken (for patients in the PopPK subset only).

7.1.6 Pharmacokinetics and population pharmacokinetics

Hercules/Herceptin® C_{min} concentrations (pre-infusion samples) will be assessed in all patients on Cycles 1, 2, 4, 6, 8, and 9. One sample at the end of infusion (C_{max}) will be collected from all patients on Cycle 1 and Cycle 6. If the Cycle 6 end of infusion sample is not feasible, a sample can be collected at the end of infusion from any Cycle 7 - 9. Additional samples will be taken from patients enrolled in the PopPK subset of Part 1. We anticipate that approximately 80 patients will need to be enrolled in this subset collection in order to obtain sufficient samples for analysis.

For patients participating in the PopPK subset, additional samples should be collected:
- Two other time points in Cycle 1 (any time on Day 2 and Day 8).
- Two randomly timed samples at 2 unscheduled visits in Cycles 2 - 8.
- One additional end of infusion C\text{max} sample in Cycle 4.

The date and time of each sample collection and of each dose administration should be carefully recorded. In order to minimize patient discomfort, PopPK sampling may be arranged at visits when the patient is attending the site for other reasons e.g., imaging, AE assessment, etc. (Refer to the Study Manual for PK sampling details).

An additional PK sample will be drawn with an immunogenicity sample should the patient experience a Hercules/Herceptin® infusion reaction.

### 7.2 STUDY DURATION

The maximum planned study duration for Part 1 of the treatment period is approximately 52 weeks which is the median PFS for first line treated MBC patients. The overall study duration for Part 1 and Part 2 is expected not to exceed 37.9 months (~163 weeks) which corresponds to the median OS for first line treated MBC. Primary and secondary endpoints will be analyzed at Week 24 in Part 1 and at Week 48 in Part 2.

The sequence and maximum duration of the study periods will be as follows:

**Screening:** Up to 28 days. See Section 13.3 for Screen Failures.

**Part 1 treatment period** (Hercules or Herceptin® plus docetaxel or paclitaxel): Hercules plus taxane or Herceptin® plus taxane will be administered for a minimum of 8 treatment cycles (1 treatment cycle = 3 weeks based on trastuzumab administration) unless the patient experiences unacceptable side effects or disease progression or is discontinued from study (see Section 9.1). Patients without a response (CR or PR) after 8 cycles can remain at the Investigator's discretion on Part 1 therapy until response or PD can be documented or is discontinued from study (see Section 9.1) or start Part 2 if a documented SD was achieved.

**Part 2 treatment period** (Hercules or Herceptin® alone until disease progression): Patients with at least SD may progress to Part 2 of the study and receive single agent Hercules or Herceptin® until disease progression, after completing a minimum of 8 cycles of treatment on Part 1 of the study.
7.3 VARIABLES AND METHODS OF ASSESSMENT

7.3.1 Efficacy

7.3.1.1 Tumor response (RECIST)

Tumor response will be assessed according to RECIST 1.1 criteria (see Appendix A) [32].

One to five target lesions (with a maximum of two lesions per organ) should be identified at baseline and recorded in the eCRF. For the purpose of this protocol, bone, CNS, and skin lesions, as well as irradiated, biopsied or surgically manipulated lesions are excluded to be measurable lesions, but are considered as non-target lesions. If radiation or manipulation is performed throughout the study, a target lesion becomes non-measurable. After radiation or manipulation to a target lesion the assessment of the patient will be limited to not evaluable or PD, unless reasonable comments justify why such lesion shall still be considered measurable. The patient or the lesion may be censored, depending on the intervention performed. Any such on-study interventions shall be discussed beforehand with the Medical Monitor.

The imaging method and settings used at baseline to document and assess a specific lesion shall be used throughout the study to consistently follow lesions according to RECIST 1.1. Details of imaging studies are provided in the Radiology Manual.

Response (CR, PR, SD, and PD) will be evaluated using the international criteria proposed by the RECIST committee.

Tumor assessments and eligibility of patients at screening will be determined by central medical imaging. To assess tumor response, a central radiology review of all images will be performed for data analysis. All routine protocol-planned imaging and any additional imaging performed due to clinical suspicion of progression (such as PET, bone scan, correlative imaging of hot-spots, etc.) should also be provided to the central review.

A central oncologist will review the clinical data, supplementing the central radiology interpretations. For example, a pleural effusion with available cytology results may be evaluated to have a benign cause. Superficial lesions, such as skin lesions and palpable lymph nodes shall be measured by a ruler or caliper. Details of any other tumor related evaluations will be provided in the eCRF. Central oncologist’s review will incorporate clinical data and non-imaging documented lesions into the response assessment.

7.3.1.2 Progression

Progression of disease is defined according to RECIST as a >20% increase in the sum of diameters of target lesions; 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. The appearance of one or more new lesions is also considered progression. A substantial
worsening of non-target lesions can be a trigger for progression. Tumor assessments are to be conducted every 6 weeks (± 3 days) up to Cycle 8, regardless of delays in treatment administration and every 12 weeks (± 3 days) Cycle 9 and beyond regardless of delays in treatment administration.

In accordance with the Council for international organizations of medical sciences (CIOMS) VI recommendations, progression of the underlying disease and its consequences will not be processed as an AE even if they lead to hospitalization or meet any other seriousness criteria including death. Rather, progression of the underlying disease and its consequences should be reported in the eCRF within no more than 48 hours. The report will include:

- Description of progression e.g., increase in the sum of diameters of target lesions, appearance of new lesions, substantial worsening of non-target lesions, or a clinically determined progression.

- Date progression was declared in accordance with FDA Guidance for Industry - Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics [23].
  - For progression based on a new lesion, the date of the first observation that the new lesion was detected.
  - If multiple assessments based on the sum of target lesion measurements are done at different times, the date of the last observation or radiological assessment of target lesions that shows a predefined increase in the sum of the target lesion measurements according to RECIST.
  - For progression based on substantial worsening of non-target lesions, the date of the first observation of substantial worsening.
  - For a clinically determined progression, the date of objectively assessed worsening.

### 7.3.1.3 Changes in Eastern Cooperative Oncology Group performance status

The ECOG scale is a 6-point categorical scale, ranging from 0 (asymptomatic) - 5 (death). The ECOG PS is evaluated at selected visits during the study and a change from baseline calculated. The ECOG score changes from baseline can then be categorized on a 3-point categorical scale: deteriorated, unchanged, and improved. Improvement or deterioration of performance status requires a decrease or an increase from baseline, respectively, of at least 1 point on the ECOG scale.

### 7.3.1.4 Extracellular domain (of HER2) fragment analysis

The analysis of soluble ECD fragments in serum will be performed at respective time points (i.e., pre-treatment, at Cycles 1, 3, 5, 7, 9, 13, and every 4 cycles thereafter, EOT and EOS) to assess their impact on PK, immunogenicity, and efficacy parameters.
7.3.2 Population pharmacokinetics

The PopPK analysis will be performed with NONMEM, Version 7.2 or later (Icon Solutions). The model will be developed with consideration of previously published population analyses using a two-compartment linear model [26, 27, 28]. Prior models and parameters may be used as Bayesian priors in the estimation of the sparse data collected in the present study.

Model development will include assessment of covariate effects on the inter-individual variability of PKs. The covariates tested will be primarily limited to those previously published in prior literature. Others may be evaluated statistically only if graphical analysis suggests a strong potential for an additional covariate effect.

The final population fixed and random effect estimates and their standard errors will be presented in tabular format. Goodness-of-fit plots, including a visual predictive check will be presented to evaluate the robustness of the final model.

Individual patient empiric Bayesian parameter estimates will be produced for each model parameter with inter-individual variability included in the model. These individual patient parameters, and the dosing histories, will be used to reconstruct the concentration time profile for each patient. From these profiles, PK parameters reflecting exposure to drug (AUC, $C_{\text{max}}$, $C_{\text{min}}$, clearance, $V_d$, and terminal elimination half-life) will be reported for each patient in the PopPK.

For details of blood sampling, processing, and storage please refer to the Study Manual.

7.3.3 Safety

Safety and tolerability will be assessed based on the nature, frequency and severity of the reported AEs, the results of laboratory assessments, physical examination and instrumental findings (e.g., ECG or LVEF).

7.3.3.1 Adverse events

The definitions and management of and special considerations for AEs are provided in Section 8.1.

7.3.3.2 Laboratory safety assessments

Samples for the following laboratory tests will be collected and analyzed locally at the time points specified in the Schedule of Activities (Table 1 and Table 2). It should be ensured that variability is minimized by using the same laboratory facility throughout the study.
Table 7-1 Laboratory Tests

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Hemoglobin total, hematocrit, red blood cell (RBC) count, RBC indices, mean, corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count (or estimate), white blood cell (WBC) count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) including differential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Chemistry</td>
<td>Albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase (LDH), uric acid.</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Prothrombin time (PT), partial thromboplastin time (PTT), International Normalized Ratio (INR)</td>
</tr>
<tr>
<td>Urinalysis (by dipstick)</td>
<td>pH, specific gravity, blood, glucose, protein, ketones</td>
</tr>
<tr>
<td>Urine pregnancy test (serum hCG at screening only)</td>
<td>For women of childbearing potential.</td>
</tr>
</tbody>
</table>

All blood samples for the scheduled safety laboratory tests must be taken before study treatment administration.

Abnormal laboratory values regardless of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1, 2, and 3 that represent a change from baseline and are assessed as clinically significant by the Investigator should be recorded as AEs. If the AE meets criteria for an SAE (see Section 8.1.4, Serious adverse event/drug reaction) it should be reported to the Sponsor within 24 hours of the investigational staff being made aware of the event’s occurrence. Determination of clinical significance is based on the Investigator's medical judgment. The following are examples of laboratory abnormalities that would be reported as AEs:

- The abnormality suggests a change in disease severity and/or organ toxicity.
- The abnormality is of a degree that requires active management; e.g., change of dose, discontinuation of the suspected causative drug, more frequent follow-up assessments, further diagnostic investigation, etc.

The following are examples of laboratory abnormalities that meet criteria required for designation as SAE:

- An elevated serum glucose that leads to hospitalization.
- A serum sodium value in the critical range that may lead to coma or death despite current patient symptom presentation (e.g., patient is asymptomatic).

Abnormal laboratory values CTCAE Grade 4 and 5 must always be reported to the Sponsor as SAE within 24 hours of the investigational staff becoming aware of the event. Grade 4 abnormalities should be reported as life-threatening only if, according to the Investigator, the patient was at risk of death at the time of the event; all other cases must be reported as medically significant SAE. Grade 5 laboratory abnormalities must always be reported as fatal SAE.
7.3.3.3 Physical examination

A complete physical examination (excluding a genitourinary examination) will be performed at the screening visit before exposure to any study treatment, and then at selected time points during the study (see schedule of assessments in Table 1 and Table 2). Vital signs and patient weight will be routinely recorded as part of the physical examination, whereas patient height will be recorded only on baseline.

7.3.3.4 Electrocardiogram

A standard 12-lead ECG will be recorded at the screening visit before exposure to any of the study treatments, and then at selected time points during the study (see schedule of assessments in Table 1 and Table 2). All ECG recordings will be identified with the patient’s number, initials, date, and time of the recording and will be recorded in the patient’s eCRF. ECG recordings will be interpreted locally and confirmed with a central analysis. In case of discrepancies in assessment between the central and local reading, the Investigator should be informed and evaluate the patient as appropriate. For details of ECG recording and transmission, please refer to the Study Manual.

7.3.3.5 Left ventricular ejection fraction

LVEF will be evaluated by MUGA or ECHO at the screening visit before exposure to any of the study treatment, and then at selected time points during the study (see schedule of assessments in Table 1 and Table 2). Please note ECHO is the preferred method. Unscheduled cardiac function tests shall be performed if the patient develops clinical signs or symptoms suspicious of LVEF dysfunction. Any new or clinically significant change from baseline should be reported as an AE or SAE as per Investigator’s clinical judgment.

It should be ensured that variability between measurements (inter-observer and intra-observer) is minimized by using the same procedures throughout the study. The same personnel and the same device should be used as much as possible to perform the assessment for an individual patient. Standardization of echocardiography should be performed in accordance the recommendations of the European Association of Echocardiography [29]. Digital storage should be performed whenever feasible in case subsequent re-evaluation is required.

7.3.3.6 Immunogenicity

Immunogenicity of Hercules and Herceptin® will be assessed using validated assays in a 3-step approach:

- Step 1: Screening,
- Step 2: Confirmatory,
- Step 3: Titer,
• A validated cell-based assay will be used to assess neutralizing antibodies (Nab) if needed.

Samples will be taken before administration of Hercules/Herceptin® since elevated antibody titer levels against Herceptin® plasma levels can interfere with the antibody assays. For details of blood sampling, processing, and storage, as well as blood volumes please refer to the Study Manual.

In case of detection of positive antibodies a correlation and analysis of the patient’s clinical and laboratory data will be performed in order to determine if there is an associated immunogenicity event (e.g., hypersensitivity or neutralizing effect).

7.3.4 Overexpression of HER2

HER2 overexpression will be performed and interpreted by a central pathohistology laboratory using the following assays, for confirmation of eligibility prior to randomization:

• IHC (Clone SP3, Thermo Fisher # RM-9103-S, Freemont, CA).
• FISH (PathVysion assay kit; Vysis Inc, Downers Grove, IL).

Interpretation will be performed in accordance with the American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for HER2 Testing in Breast Cancer [3].

Sample from either a paraffin-fixed formalin-embedded primary tumor or metastatic tissue core biopsy may be used. As IHC or FISH (performed if IHC is 2+) may not be possible from primary tumor sample due to variability of fixation and embedding procedures used locally, sampling of metastasis core biopsy is strongly encouraged whenever possible. For details of sample fixation, embedding, and shipment, please refer to the Study Manual.

7.3.5 Tumor and endocrine status

Tumor and endocrine status will be performed and interpreted by a central pathohistology laboratory. The same tumor sample as the one used for HER2 assessment will be used for assessing progesterone and estrogen tumor status. Please refer to the Laboratory Manual for details on sampling and shipping procedures.

8 ADVERSE EVENTS

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as outlined in this section.

The Investigator must pursue and obtain information adequate both to determine the outcome of all AEs and to assess whether it meets the criteria for classification as an SAE
requiring immediate notification to Mylan or its designated Representative. The Investigator is required to assess causality and should obtain sufficient information to determine the causality of all AEs. \textit{All AEs will be followed-up until resolution, until the event is resolved, is deemed to be stable or until the event is found to be due to another known cause (concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted with the Sponsor concurring with that assessment.}

Any non-serious AE that is determined by the Medical Monitor/Sponsor to be serious will be managed by the Sponsor or its designated Representative as an SAE as part of ongoing safety reviews conducted by the Sponsor. To assist in the determination of case seriousness further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical trial.

\section{8.1 DEFINITIONS}

\subsection{8.1.1 Adverse events}

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with, whether or not related to the product.

The above definition covers also cases of

- Exacerbation of pre-existing diseases or conditions.
  - Pre-existing diseases or conditions (reported at time of screening in medical history) will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition.

Only overdose of study drugs (>10\% of protocol calculated dose) will be recorded as a protocol deviation and an adverse event. In addition, signs, symptoms, or the clinical sequelae of overdose will be recorded as AEs in the eCRF and if serious notified to Mylan within 24 hours per section 8.2.6.

Study drug administered at doses that deviate \( \leq 5\% \) from the protocol calculated dose should not be recorded as deviations.

Events occurring in patients treated with the active comparator or during treatment free periods of the study are also considered AEs. An AE is defined as treatment emergent if the first onset or worsening is after the first administration of Hercules or Herceptin®.

\subsection{8.1.2 Adverse drug reaction}

All noxious and unintended responses to an investigational product related to any dose of the investigation products should be considered adverse drug reactions (ADRs). The phrase “responses to an investigational product” means that a causal relationship between
an investigational product and an AE is at least a reasonable possibility. All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to an investigational product will be designated as ADRs.

All AEs, with the causal relationship to the study drug reported as “possible”, “probable” or “definite” will be considered ADRs. If the relationship to the study drug is not given, then the AE must be treated as if the relationship were “possible.”

**8.1.3 Unexpected adverse event/adverse reaction**

An expected AE or adverse reaction (AR) is defined as one whose nature or severity is consistent with the applicable product safety described in the IB. For the marketed product Herceptin® full details concerning its safety profile are also provided by the relevant SmPC in the IB for Hercules.

For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. Reports that add significant information on specificity or severity of a known, already documented AR constitute unexpected events. Examples would be (a) acute renal failure as an expected AR with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected).

**8.1.4 Serious adverse events/drug reaction**

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
  - Note: Death due to progression of the underlying disease will not be processed as an expedited report. Rather, it should be reported in the eCRF within no more than 48 hours of occurrence. (see Section 7.3.1.2)
  - Is life-threatening.
    - NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at 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.
  - Results in persistent or significant disability/incapacity.
  - Is a congenital anomaly.
NOTE: A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is considered an SAE. However, a newly diagnosed pregnancy in a patient that has received the study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy. The patient with newly diagnosed pregnancy will discontinue receiving study treatment and will be followed-up every 3 months until delivery or termination to gather information about the outcome of the pregnancy.

- Is an important medical event.

NOTE: Important Medical Event: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Requires inpatient hospitalization or prolongation of existing hospitalization.

NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the test drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.

Events NOT to be reported as SAEs are hospitalizations for the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.

- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen.

- Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care).

- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

- Admission exclusively for the administration of blood products.

Hospitalization also does not include the following:

- Rehabilitation facilities.
- Hospice facilities.
- Respite care (e.g., caregiver relief).
- Skilled nursing facilities.
- Nursing homes.

### 8.2 MANAGEMENT OF ADVERSE EVENTS

The active reporting period for SAEs will be from the time the patient signs the ICF until the EOS visit. The active reporting period for AEs will be from the time the patient receives the first dose until the EOS visit. However, SAEs should be reported any time after the active reporting period, when the Investigator becomes aware and the SAE is considered to be reasonably related to the study drug. All SAEs should be immediately (24 hours) reported as per Section 8.2.6.

#### 8.2.1 Collection

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as described previously. At each visit, the patient will be allowed time to spontaneously report any issues since the last visit or evaluation. The Investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as

- “How are you feeling?”
- “Have you experienced any issues since your last visit?”
- “Have you taken any new medications since your last visit?”

Any clinically relevant observations made during the visit will also be considered AEs.

#### 8.2.2 Evaluation

**8.2.2.1 Severity assessment of adverse events**

The clinical severity of an AE will be graded whenever possible using the NCI-CTC AE Criteria Version 4.03 [19]. A copy of these criteria will be provided to each study site. If an AE is not listed in the CTCAE, its clinical severity will be classified as follows:
Table 8-1  Clinical Severity of Adverse Events

If required on the AE case report forms (CRFs), the Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - MILD</td>
<td>Does not interfere with patient's usual function.</td>
</tr>
<tr>
<td>2 - MODERATE</td>
<td>Interferes to some extent with patient's usual function.</td>
</tr>
<tr>
<td>3 - SEVERE</td>
<td>Interferes significantly with patient's usual function.</td>
</tr>
<tr>
<td>4 - LIFE-THREATENING</td>
<td>Risk of death at time of event</td>
</tr>
<tr>
<td>5 - DEATH</td>
<td>Death related to AE</td>
</tr>
</tbody>
</table>

If an AE is Graded 4 or 5 according to the above criteria, then the AE meets the criteria for an SAE and the Investigator should immediately notify the Sponsor or designee as described in Section 8.2.6.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity based on the CTCAE grading or on the above Table 8-1, whereas an SAE is an AE that meets any of the regulatory specified criteria required for designation as seriousness described in Section 8.1.4.

8.2.2.2  Action taken

The undertaken actions for an AE are described in Table 8-2:

Table 8-2  Action Taken for an Adverse Event

<table>
<thead>
<tr>
<th>Action Taken</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose reduced (only allowed for docetaxel)</td>
<td>The dose regimen was reduced by changing its frequency, strength, or amount.</td>
</tr>
<tr>
<td>Dose increased</td>
<td>The dose regimen was increased by changing its frequency, strength, or amount.</td>
</tr>
<tr>
<td>Treatment interrupted</td>
<td>The treatment was temporarily interrupted.</td>
</tr>
<tr>
<td>Treatment withdrawn</td>
<td>The treatment was permanently discontinued.</td>
</tr>
<tr>
<td>Concomitant therapy or procedures</td>
<td>Treatment was needed as a result of the AE (the concomitant treatment should be recorded on the relevant page of the eCRF).</td>
</tr>
<tr>
<td>Unknown</td>
<td>Not known, not observed, not recorded, or refused.</td>
</tr>
<tr>
<td>No action taken</td>
<td>The AE did not require any intervention.</td>
</tr>
<tr>
<td>Not applicable</td>
<td></td>
</tr>
</tbody>
</table>

8.2.2.2.1  Outcome at the time of last observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved.
- Recovered/resolved with sequelae.
- Recovering/resolving.
Not recovered/not resolved.

Fatal*.

Unknown.

All ongoing AEs without fatal outcome will be recorded as not recovered/not resolved at the time of death.

*Only select fatal as an outcome when the AE results in death. If more than one AE is possibly related to the patient’s death, the outcome of death should be indicated for the AE which is the most plausible cause of death in the opinion of the Investigator. Note: although “fatal” is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

### 8.2.2.3 Causality assessment of adverse events

An Investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. The Investigator must make an assessment of the relationship of each AE (serious and non-serious) to the study treatment(s) and record this relationship in the CRF.

In addition, if the Investigator determines an AE or SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, as appropriate, and report the assessment in accordance with the reporting requirements, as applicable, AE or SAE.

Factors that need to be considered when making a causality assessment include:

- Temporal relationship (e.g., time of onset).
- Clinical and pathological characteristics of the event(s).
- Pharmacological plausibility.
- Exclusion of confounding factors (medical and medication history).
- Drug Interactions.
- De-challenge/re-challenge.
- Dose relationship.

A suspected relationship (definite, probable, possible) between the events and the study medication means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality. The Investigator is responsible for assessing relationship of AEs to study treatment in accordance with the following definitions:
### Table 8-3 Definition of Suspected Relationship between the Events and Study Medication

| DEFINITELY | Causal relationship is certain | For Example: the temporal relationship between drug exposure and the adverse event (AE) onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary. |
| PROBABLY   | High degree of certainty for causal relationship | For Example: the temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely. |
| POSSIBLY   | Causal relationship is uncertain | For Example: the temporal relationship between drug exposure and the AE onset/course is reasonable or unknown, de-challenge information is either unknown or equivocal, and while other potential causes may or may not exist, a causal relationship to study drug does not appear probable. |
| UNLIKELY   | Not reasonable related although a causal relationship cannot be ruled out |  |
| UNRELATED/NOT RELATED | No possible relationship | The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible. |

If the relationship to the study treatment(s) is consider to be unlikely or not related, an alternative suspected etiology should be provided (e.g., concomitant medications, intercurrent events).

### 8.2.3 Documentation

All AEs occurring within the period of observation for the study must be documented in the eCRF with the following information; where appropriate (the period of observation for the study is described in Section 8.2):

- AE name or term in standard medical terminology.
- When the AE first occurred (start date and time); SAE start date is defined as the date the AE became serious.
- When the AE stopped (stop date and time or date and time of last observation if ongoing, i.e., recovering or not recovered).
- Severity of the AE.
- Seriousness (hospitalization, death, etc.).
• Actions taken (Description of action taken in treating the AE and/or change in study drug administration or dose).

• Outcome.

• Investigator’s opinion regarding the AE relationship to the study treatments.

• When the AE stopped (stop date and time).

AEs on-going at the end of Part 1 will be marked as ongoing and followed-up in Part 2.

8.2.4 Treatment of adverse events

AEs that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the study treatment should be temporarily interrupted and the reason documented in the eCRF. The decision about whether the patient may resume the study treatment will be made by the Sponsor after consultation with the Investigator and/or Medical Monitor.

Emergency unblinding of the treatment is not likely to be necessary in this study, even in case of SAEs. However, if in emergency the Investigator determines that unblinding for an individual patient is necessary, he/she should follow the procedures described in Section 5.2 (Blinding and Unblinding Treatment Assignment).

8.2.5 Follow-up

Any AE will be followed-up to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the patient’s medical record and recorded on the appropriate eCRF page.

8.2.6 Notification

For SAEs, the active reporting period to Mylan or its designated Representative begins from the time that the patient provides informed consent, which is obtained prior to the patient’s participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Should an Investigator be made aware of any SAE occurring any time after the active reporting period, the SAE must be promptly reported to Mylan only in case of reasonable causality.

The SAE Reporting Form is to be completed for all serious AEs and other relevant special situations as described below, signed by the Investigator, and emailed or faxed with supporting documentation (e.g., CRFs, hospital records, laboratory reports). Patient identity details (such as but not limited to name or clinic/hospital number) must not be visible on SAE forms or any supporting documentation provided by the Investigator.
These should be “blacked out”, signed and dated before submission to Mylan or its
designee. **The subject ID must be provided on every document.**

**Email is the preferred method of communication.**

**All SAEs must be notified within 24 hours to:**

**Global Product Safety & Risk Management**
Mylan
Albany Gate, Potters Bar
United Kingdom, EN6 1AG

PV MAIL HUB FOR IMMEDIATE SAFETY REPORTS:
Her3001-PV-Hub@mylan.com

In case an acknowledgment is not received within 24 hours, forward via
Fax: +1-304-285-6409 or Tel: +44 (0)1707 853 000

At that time of first notification, the Investigator/designee should at least provide the
following information:

- Protocol number
- Reporter (Study site and Investigator)
- Suspected study treatment
- Patient’s study number
- SAE term
- The seriousness criteria that were met
- Investigator’s opinion of the relationship to the study treatments

And if available:

- Severity
- Patient’s age
- Date of first dose of study treatment
- Date of last dose of study treatment, if applicable
- Start and stop of the event (date and time)
- A brief description of the event, outcome to date, and any actions taken
- Concomitant medication at onset of the event
- Relevant past history information
- Relevant laboratory test findings
• Whether and when the Investigator was unblinded to the patient’s treatment assignment

If the initial notification of an SAE is by telephone, within 24 hours of the initial telephone notification the Investigator must email the written SAE Report Form that describes the SAE to the Mylan Global Product Safety and Risk Management as listed in Appendix B.

The Investigator may be requested by Mylan/designee to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Mylan or its designated representative.

Any missing or additional relevant information concerning the SAE should be provided on a follow-up SAE Report Form. Ensure that any additional information requested by Sponsor or designee about the event, as outlined above (e.g., hospital reports, autopsy report) is provided to Sponsor/designee as soon as it is available.

The Investigator is required to comply with applicable regulations (including local law and guidance) regarding notification to her/her RA, Ethics Committees (ECs) and institutions.

All AE Reporting, including suspected serious unexpected AEs will be carried out in accordance with acceptable local regulations

Suspected unexpected serious adverse reactions (SUSARs), SAEs or other cases as required by the concerned competent Authorities and ECs will be reported by the Sponsor/Representative to all concerned parties within applicable timelines. The Sponsor/Representative will also submit periodic safety reports (e.g., Development Safety Update Reports) as required by international regulations.

8.3 SPECIAL CONSIDERATIONS

The Investigator should report pregnancy and AEs of special interest (as described in Sections 8.3.1 and 8.3.2) within 24 hours even if these do not meet any of the seriousness criteria and followed until a final outcome is determined (e.g., parturition, spontaneous or scheduled termination. The Investigator should contact Mylan Global Product Safety and Risk Management (see Appendix B) and record relevant information on the appropriate form provided by the Sponsor or Sponsor’s Representative. Overdose, medication errors and other events included in the definition provided in Section 8.1.1 should be reported as per Section Error! Reference source not found., while progression of the underlying disease and its consequences should be reported according to Section 8.3.3
8.3.1 Adverse event of special interest

All AEs leading to premature discontinuation of trastuzumab (Hercules/Herceptin®) (e.g., including but not limited to cardiomyopathy or immunological reactions) are considered AEs of special interest and to be reported on the SAE Reporting Form by designating AE of special interest. Examples of such events (but not limited to those events) are given in Section 5.5, Dose Modification.

8.3.2 Pregnancy

All patients of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Patient should be instructed to contact the Investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted throughout the study, as detailed in the schedule of assessments in Table 1 and Table 2. A woman who is found to be pregnant at the screening visit will be excluded from the study and will be considered to be a screening failure. A woman who becomes pregnant during the study will be immediately discontinued from study treatment. A male that has a partner that becomes pregnant during the study will not be discontinued from study treatment. Early termination visit assessments are required as soon as possible after learning of the pregnancy. This information should be captured in the pregnancy form and reported to Mylan Global Product Safety and Risk Management within 24 hours from the time of initial awareness, even beyond the closure of the clinical database.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or an SAE. A spontaneous abortion is always considered to be a SAE and will be reported to the Sponsor.

Elective termination (i.e., without medical reasons) of an uncomplicated pregnancy is considered to be an elective procedure and not an AE; nevertheless, Mylan requests that the outcome (e.g., elective termination) be reported within 24 hours and sent as a follow-up on the Delivery and Infant Follow-up Form).

The Investigator is also responsible for following up the pregnancy at 3 monthly intervals until delivery or termination, informing the Sponsor about its outcome.

Exposure during pregnancy

For investigational and for marketed products, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or being exposed (e.g., due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product.
• A male has been exposed (e.g., due to treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner’s pregnancy.

In the case of paternal exposure, the Investigator will provide the study patient with the Pregnancy Reporting Form to deliver to her partner and document per instructions that this information was provided to her partner.

8.3.3 Progression of the underlying disease and its consequences

In accordance with the Council for International Organizations of Medical Sciences (CIOMS) VI recommendations, progression of the underlying disease and its consequences will not be processed as AEs even if they lead to hospitalization or meet any other seriousness criteria including death. Rather, progression of the underlying disease and its consequences should be reported in the eCRF within no more than 48 hours.

9 PATIENT WITHDRAWAL

9.1 PREMATURE PATIENT WITHDRAWAL

All patients will be informed that they have the right to withdraw from treatment, study or follow-up at any time, for any reason, without prejudice, and without having to justify their reasons or decisions. Additionally the Investigator may discontinue the treatment of a patient at any time if he or she considers this to be in the patient's best interest.

Specifically, treatment should be discontinued if any of the following reasons apply (but not limited to):

• Severe infusion response to Hercules or Herceptin® or taxane (e.g., anaphylaxis and severe hypersensitivity reactions characterized by dyspnea requiring treatment, angioedema, and generalized urticarial rash).

• Any other physical examination finding, change in vital signs, AE or laboratory abnormality that in the opinion of the Investigator, would cause an excessive risk if the patient continues the study.

• Pregnancy. If pregnancy occurs in a female patient, the patient will be discontinued from study and followed until the outcome of the pregnancy is known.

• Unacceptable toxicity (see Section 5.5).

• Worsening LVEF, as defined in Dose Modification Section 5.5 or intercurrent illness preventing continued treatment.

• Patient indicates unwillingness to comply with study treatment or protocol requirements or is lost to follow-up.

• Patient withdraws from study.
• Use of prohibited therapy (as defined in Prohibited Therapy Section 6.2).
• Disease progression.
• Non-compliance that in the opinion of the Investigator will compromise possible response to therapy.
• Patient enters the study in violation of the protocol.
• In the Investigator’s opinion it is in the patient’s best interest to discontinue treatment, e.g., changes in medical or social condition.
• Administrative reasons, such as inability of the patient, the Investigator or the Sponsor to continue the study.

Investigators must attempt to contact (by telephone or other means) patients who fail to attend scheduled visits, to exclude the possibility of an AE being the cause of withdrawal. All AEs must be documented in the source documentation and eCRF, reported, and followed up as described in Section 8. When a patient is “lost to follow-up”, a reasonable effort, comprised of no less than 3 documented phone calls on separate occasions and certified mail letter, should be made to contact the patient to determine a reason for a failure to return. If following these actions, the patient fails to be contacted or fails to return to the clinic; the patient should be identified as “lost to follow-up” in the eCRF.

After premature discontinuation of treatment, the Investigator should attempt to collect the survival information as dictated by the Schedule of Assessments. For details please see Follow-up of prematurely discontinued patients Section 7.1.4.

Patients discontinued from the study will not be replaced.

10 DATA ANALYSIS/STATISTICAL METHODS

10.1 SCHEDULE OF ANALYSES

The primary analysis will be performed in Part 1. This analysis will include the primary efficacy endpoint, safety, and the PopPK. These data may be used for regulatory submission. To preserve the integrity of the analysis for the secondary endpoints the results will be kept confidential to all personnel directly involved in the performance of the trial.

The supplementary analysis will be performed in Part 2 on all secondary efficacy endpoints and the cumulative safety data. In addition, sensitivity analyses will be performed.

One interim analysis on primary efficacy endpoint is planned and described in Section 10.6.
10.2 SAMPLE SIZE DETERMINATION

Final sample size may be up to 600 patients randomized. The rationale is described in the following paragraphs.

A sample size of 410 patients (205 per treatment group) in Protocol Amendment 2 is required to provide at least 80% power to declare Hercules equivalent to Herceptin® in the analysis of ORR at Week 24. This sample size assumes that both treatment groups will exhibit an ORR of 69% at Week 24 and that the ratio of Hercules to Herceptin® will be analyzed with a two-sided 90% CI. If the 90% CI falls wholly within an equivalence region defined as (0.81, 1.24), then equivalence will be declared. The equivalence region was justified by performing a fixed-effects meta-analysis with historical Herceptin® trials to estimate the treatment effect of Herceptin plus chemotherapy versus chemotherapy alone.

To arrive at the planned number of patients, the required sample size of 410 was increased to 456 to reflect an approximate 10% attrition rate. It is expected that, at most, 10% of the randomized patients in Protocol Amendment 2 and beyond will be lost-to-follow-up.

Final sample size will be determined at the interim analysis using the sample size re-estimation approach described in the SAP and may increase up to 600.

10.3 ANALYSIS POPULATIONS

The following four analysis populations are planned for this study:

- **Intention-to-treat (ITT) population**: All patients randomized.
- **Safety Population (SAF)**: All patients who had received at least one dose of Hercules/Herceptin®.
- **Per-protocol (PP) Population**: All patients in the ITT population who started treatment without major protocol deviations as defined in the statistical analysis plan (SAP) and finally decided in a Blind Data Review Meeting before database lock for study Part 1. In particular patients will be excluded from the PP population if they:
  - Have anti-trastuzumab antibodies at baseline.
  - Drop out for other reasons than PD with less than 2 complete cycles of therapy received.
  - Have no baseline or post-baseline tumor assessment.
- **Pharmacokinetic (PK) population**: All randomized patients who received at least one dose of Hercules/Herceptin® and who provided at least one post dose sample for PK analysis.
The primary efficacy analysis will be based on the ITT population of patients in Protocol Amendment 2. The efficacy evaluation in the PP set and the full ITT set (which is comprised of all randomized patients) will also be reported in sensitivity analyses. The PopPK analysis will be based on the PK population. The analysis of safety will be based on the SAF Population.

10.3.1 Stratification

Stratification factors that will be taken into account in the secondary analyses are the following:

- Tumor progression into metastatic phase \( \geq 2 \) years OR \(< 2 \) years after primary diagnosis (calculated as time from primary tumor surgery until randomization). Patients diagnosed with primary metastatic disease will be classified together with the patients who progressed <2 years, regardless of the date of tumor surgery.
- ER/PgR status (ER and/or PgR positive/ER and PgR negative).
- Type of taxane received (e.g., paclitaxel or docetaxel). Investigator’s discretion at the site level prior to the start of screening.

10.4 STATISTICAL ANALYSES

Unless otherwise specified, descriptive data summaries will be tabulated by treatment for all endpoints. Categorical outcomes will be summarized by number and percent of patients that fall into each category. For continuous outcomes, descriptive statistics include number of subjects (n), arithmetic mean, standard deviation, minimum, median, maximum, and 95% CIs of the means. Kaplan-Meier estimates will be provided for time-to-event endpoints. Where data are collected over time, both the observed data and the change from baseline will be summarized at each visit.

In addition to the outline of statistical analysis as given below a detailed SAP will be prepared and finalized before unblinding.

10.4.1 Analysis of efficacy

10.4.1.1 Primary efficacy analysis

The primary efficacy endpoint is the best ORR where objective response is defined as a CR or PR according to RECIST 1.1 based on central tumor evaluation (see Table 1).

The ratio of the best ORRs at Week 24 will be statistically compared with the following hypotheses:

\[
\begin{align*}
\text{Ho: } \frac{\text{RT}}{\text{RC}} & \leq 0.81\% \text{ or } \frac{\text{RT}}{\text{RC}} \geq 1.24 \\
\text{H1: } 0.81 & < \frac{\text{RT}}{\text{RC}} < 1.24,
\end{align*}
\]
where RT and RC are the best ORR of Test (Hercules) and Control (Herceptin®), respectively.

A two-sided 90% CI for the ratio of the best ORRs will be calculated based on the method of logarithmic transformation with no adjustment for covariates. The two-sided 90% CI is equivalent to two one-sided tests (TOST) at the 5% level. Equivalence will be declared if the CI is completely within the equivalence range of ([0.81, 1.24]).

Only patients with measurable disease at baseline will be included in the analysis of the objective response.

10.4.1.2 Secondary efficacy analyses

10.4.1.2.1 Time to tumor progression

TTP is defined as the time from randomization to date of first documentation of objective progression.

Patients last known to be 1) alive 2) on treatment or within 28 days after discontinuation of treatment and 3) progression-free are censored at the date of the last objective disease assessment that verified lack of disease progression. Patients with no disease assessments or inadequate baseline disease assessments are censored at the start date. Patients who die prior to objective progression while on treatment are censored at the date of last objective tumor assessment prior to death. Patients with at least one on-study disease assessment who discontinue treatment without disease progression are censored at the date of the last objective disease assessment. Patients with documentation of progression after an unacceptably long interval (2 or more missed or indeterminate assessments) since the last tumor assessment will be censored at the time of last objective assessment without progression. Kaplan-Meier plots by treatment will be presented and the log-rank test of the two treatment groups unadjusted for any covariates will be performed. Cox’s proportional hazards model will be used to analyze for treatment effects, adjusting for each of the stratification factors. Hazard ratios and 95% CIs will be presented. The analysis will be performed at Week 24 and 48 for Part 1 and Part 2, respectively, for the ITT population.

10.4.1.2.2 Progression free survival

PFS is defined as the time from randomization to first documentation of objective progression or to death due to any cause. Patients last known to be: 1) alive 2) on treatment or typically 28 days of discontinuation of treatment and 3) progression-free, are censored at the date of the last objective disease assessment that verified lack of disease progression. Patients with inadequate baseline disease assessment are censored at the start date. Patients with no on-study disease assessments are censored at the start date unless death occurred prior to the first planned assessment (in which case the death is an event). Patients with at least one on-study disease assessment who discontinue treatment without documented disease progression and without death are censored at the date of the last
objective disease assessment (with objective status CR, PR or Stable). Patients with documentation of progression or death after an unacceptably long interval (2 or more missed or indeterminate assessments) since the last tumor assessment will be censored at the time of last objective assessment without progression. PFS will be analyzed in the same manner as TTP.

10.4.1.2.3 Overall survival

OS is defined as the time from date of randomization to date of death due to any cause. Patients last known to be alive are censored at date of last contact. OS will be analyzed in the same manner as TTP.

10.4.1.2.4 Duration of response

DR is defined as the time from the first documentation of objective response until the date of first documentation of objective progression or to death due to any cause. The censorship of DR is the same as that of PFS.

DR will be analyzed in the same manner as TTP at Week 48 only. Only responders will be included in the analysis.

10.4.1.3 Sensitivity analyses

The following sensitivity analyses will be performed on the primary endpoint, ORR:

- Subgroup analyses by age, ethnic origin, time from initial diagnosis of metastatic disease, previous adjuvant/neoadjuvant chemotherapy or HER2 targeted treatment, and geographic region as detailed in the SAP.
- Cochran-Mantel-Haenszel analysis stratified by the stratification factors will be performed. Estimates of the relative risk and the odds ratio and their 90% and 95% CIs will be presented.
- Logistic regression analysis of the treatment odds ratio adjusted for the stratification factors will be performed.
- The primary efficacy analysis will be replicated in the PP population.
- The primary efficacy analysis will be replicated in the full ITT set (which is comprised of all randomized patients).

Sensitivity analyses for the secondary endpoints of PFS and OS will also be conducted. Description of these analyses and any other sensitivity analyses will be described in the SAP.

10.4.1.4 Population pharmacokinetics

The purpose of the PK analysis in this study is to characterize similarity in the PKs of trastuzumab following administration of each of the two study treatments. PopPK analysis will be performed with NONMEM, Version 7.2 or later (Icon Solutions). The
model will be developed with consideration of previously published population analyses using a two-compartment linear model [26, 27, 28]. Prior models and parameters may be used as Bayesian priors in the estimation parameters from the sparse data collected in the present study. Methods are briefly mentioned in this protocol, but will be described in detail in a PopPK Analysis Plan.

- Observed $C_{\text{min}}$ values at the end of the first cycle and on the pooled data of Cycles 6 - 8, will be used to assess the similarity of Hercules vs. Herceptin®, using a statistical approach for bioequivalence.

- Descriptive presentation of key PopPK parameters will be summarized (i.e., clearance, inter-compartmental clearance, central and peripheral distribution volumes).

- Assessment of the potential impact of soluble HER2/ECD presence on trastuzumab PK levels will be evaluated.

**Graphical exploration:** A graphical exploration of the concentration vs. time data will be conducted to provide a visual inspection of the kinetic profile of Herceptin® vs. Hercules and to guide the modeling process. Plots may be stratified by levels of categorical covariates. Additional graphical analysis will be performed using the results of the base model to evaluate potential explanatory covariates.

**Structural pharmacokinetic model:** A structural model consistent with the published literature will be the starting place for structural model development. A two-compartment linear model will be described. The parameters estimated will be clearance, $V_d$ of the central compartment, inter-compartmental clearance, and $V_d$ for the peripheral compartment.

**Models for inter-individual (Level 1) and residual variability (Level 2) random effects:** In order to characterize the inter-individual variability in Herceptin® and Hercules PKs, the PK parameters clearance and volume of the central compartment will initially be assigned log-normally distributed random effects. The appropriateness of this model assumption will be evaluated by the test of location of etas provided in NONMEM, and through graphical analysis. An attempt to add IIV to additional structural parameters will be explored, but may not be feasible based on the sparseness of the data. Residual variability will be modeled initially with a constant coefficient of variation model.

**Covariate model:** Potentially influential covariates will be evaluated using a forward selection followed by backward elimination process. The evaluated covariates may include those reported as significant in prior publications of trastuzumab PKs. These include alkaline phosphatase, number of metastatic sites, ECD, and body weight. Covariates may be utilized as repeated measures with values changing across the duration of the study.
Maximum likelihood parameter estimation:

First-order conditional estimation methods will be used initially for parameter estimation. Alternative methods may be used if warranted by the data (e.g., Stochastic Approximation Expectation Maximization (SAEM), or importance sampling).

Individual patient empiric Bayesian parameter estimates will be produced for each model parameter with inter-individual variability included in the model. These individual patient parameters, and the dosing histories, will be used to reconstruct the concentration time profile for each patient. From these profiles, PK parameters reflecting exposure to drug (AUC, C_max, C_min, clearance, V_d, and terminal elimination half-life) will be reported for each patient in the PopPK.

Only descriptive and exploratory statistics are planned; the conceptual framework for bioequivalence trials will not be applied formally, as this is a secondary endpoint of the study and 100% bioavailability is assumed for I.V. agents.

A stepwise modeling approach, with iterative inspections of results and graphical representation to monitor the search for the best model will be undertaken. A flow diagram of the analysis performed and representative control/command files for each significant model building/reduction step will be provided in the PK study report.

10.4.2 Safety and tolerability analyses

The safety analysis will be based on the SAF population that is any patient who has received at least one dose of IMP. Additional post-hoc analyses may be required depending on the safety information emerging from the following standard assessments:

10.4.2.1 Adverse events

All reported AEs will be assigned the system organ class and preferred term according to Medical Dictionary for Regulatory Activities (MedDRA), and graded by CTCAE Version 4.03. Listing of all AEs will be tabulated by treatment groups and by system organ class and preferred term.

Treatment-emergent adverse events (TEAE) are defined as any AE which started or deteriorated at or after treatment with the IMP (Hercules/Herceptin®) but on or within 28 days following the last dose of IMP.

Patient incidence of the following AEs will be tabulated by treatment groups and by system organ class and preferred term:

- All TEAEs by worst grade.
- Grade 3 or higher TEAEs.
- SAEs.
• Treatment-related AEs.
• Treatment-related SAEs.
• TEAEs leading to discontinuation of IMP.
• TEAEs leading to interruption of IMP.
• TEAEs leading to removal from the study.
• Fatal AEs.

In addition, the exposure-adjusted incidence rates of selected categories of AEs may be tabulated by treatment group.

10.4.2.2 Clinical laboratory evaluations

For hematology and biochemistry variables, descriptive summaries of observed values and changes from baseline will be presented by treatment arm.

Each abnormal value will be flagged to show whether it is a value below or above the reference range. For the assessment of laboratory variables, 5 categories will be used that take into account the Investigator’s assessment of clinical relevance:

• Clinically relevant, above.
• Not clinically relevant, above.
• Within.
• Not clinically relevant, below.
• Clinically relevant, below.

The assessments of laboratory variables will be tabulated by visit for each clinical laboratory parameter by treatment arm (frequency tables). Additionally, for each laboratory parameter, shifts in assessments from baseline to all post-baseline visits will be presented by treatment arm (shift tables).

If National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grades are available for a clinical laboratory parameter they will be determined according to CTCAE version 4.03 and used to present frequency and shift tables based on NCI-CTC grades rather than categories of abnormality. Patient listings of Grades ≥3 laboratory toxicities will be provided.

Laboratory values that are outside the reference range will also be flagged in the data listings, along with corresponding reference ranges.

The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter by treatment arm (frequency tables). Additionally, for each of these urine
parameter shifts in assessments from baseline to all post-baseline visits will be presented for each treatment arm (shift tables).

10.4.2.3 Vital signs

Descriptive summaries of observed values and changes from baseline will be calculated for vital signs and ECOG PS. These summaries will be presented by visit and treatment arm.

10.4.2.4 Electrocardiograms

Descriptive summaries of observed values and changes from baseline will be calculated for ECG variables. QT will be corrected according to Bazett formula. Frequency and shift tables will be presented for the classified values of QTc as given by International Conference on Harmonization (ICH) E14 as well as for the overall clinical assessment. The ICH-E14 classifications are as follows:

- Absolute QTc interval prolongation:
  - QTc interval >450.
  - QTc interval >480.
  - QTc interval >500.

- Change from baseline in QTc interval:
  - QTc interval increases from baseline >30.
  - QTc interval increases from baseline >60.

10.4.2.5 Left ventricular ejection fraction

Descriptive summaries of observed values and changes from baseline will be calculated for LVEF. These summaries will be presented by visit and treatment arm.

10.5 INDEPENDENT DATA AND SAFETY MONITORING BOARD

Independent oversight of this study will be provided by a DSMB, a multidisciplinary group with expertise in the fields of oncology, clinical immunology, and statistics. The DSMB consists of a minimum of 3 members who have no direct role in the conduct of this clinical trial, or any other conflict of interest, and operate based on the relevant Charter. The DSMB will review partially unblinded interim and cumulative safety and blinded efficacy data, on a quarterly basis with ad hoc meetings scheduled as necessary. The DSMB will be informed of any significant safety findings in an ad hoc fashion and additional information provided to them at their request if further review is needed. The DSMB will review partially unblinded efficacy data at the a priori declared interim analysis. The DSMB is empowered to access partially unblinded information at any time and recommend 5 courses of action with respect to continuing the study:

- The study should continue without modification.
- The study should continue but with modification to the protocol or with additional data presentation needs.
- The study should be temporarily suspended to further enrollment and treatment administration, pending further evaluation of data.
- The study should be terminated because of safety concerns; or
- The study should be terminated because of lack of efficacy.

The responsibility for the final decision regarding the DSMB-recommended course of action will rest with Sponsor. Details will be described in the DSMB Charter.

10.6 INTERIM ANALYSIS

A formal interim analysis will be overseen by the DSMB when at least 30% of the information target is available. The sample size will be re-estimated at this analysis based on the interim data. In addition, the futility analysis will be carried out. The study may be stopped for futility if pre-specified futility boundaries are met. The details will be described in the SAP.

10.7 MULTIPLE COMPARISON ADJUSTMENTS

No multiple comparison adjustment for the Part 1 primary analysis is required. All other efficacy analyses in Part 1 or 2 will not be adjusted for multiplicity.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and its designees will perform quality control checks on this clinical study to assure the accuracy and reliability of study related data including the selection of qualified Principal Investigators and appropriate study centers, review of protocol procedures with the Principal Investigators and associated personnel, and periodic monitoring visits conducted by the Sponsor or Sponsor Representative.

Data will be entered into the clinical study database and verified for accuracy, following procedures defined by the Sponsor, or designee. Data will be processed and analyzed following procedures defined by the Sponsor, or designee.

This study will be subject to audit by the Sponsor or designee at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the Study Protocol; ICH, Good Clinical Practice (GCP) E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity and enrolment rate. The Sponsor or designee may conduct audits on any selected study sites, requiring access to patient notes, study documentation, and facilities or laboratories used for the study.
The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for EC or RAs according to GCP guidelines. The Investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRF print-outs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a RA informs the Investigator that it intends to conduct an inspection, the Investigator shall notify the Sponsor immediately.

### 11.1 STUDY MONITORING

The study will be initiated by the monitor, or designee, during an on-site visit after all required documents have been processed. Qualified clinical monitors will perform on-site monitoring visits as frequently as is deemed necessary.

During the site visit, the monitor will compare the data entered into the eCRF with the source documents. The first visit after initiation will usually be made as soon as possible after enrollment has started. At these visits, the monitor will compare the data entered onto the eCRFs with source documents. Source documents include, but are not limited to: original documents, data and records such as hospital/medical records, clinic charts, lab results, patient diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc.). At a minimum, all data required to be collected by the protocol shall be recorded in source documents first and then entered into the eCRF (unless otherwise specified). The monitor will review and verify: the diagnosis, medical history, inclusion/exclusion criteria, physical exams and vital signs, efficacy evaluations; safety and laboratory evaluations/tests, AEs and SAEs, concomitant medications and procedures, and the use of study drug. Specific items required as source documents will be reviewed with the Investigator prior to the study.

In addition, the monitor will verify that standards of GCP were followed. This includes, but is not limited to: completion of regulatory documents (e.g., FDA Form 1572, financial disclosure, Institutional Review Board [IRB]/Independent Ethics Committee [IEC] approvals, submitting safety/progress reports, etc.) ensuring Informed Consent was adequately performed and documented, that study drug dispensation and accountability was handled properly, SAEs were reported to the Sponsor and IRB/IEC in a timely manner, that the protocol was followed and that the rights and welfare of patients were protected.

Findings from the review of CRFs/eCRFs, source documents, and study conduct will be discussed with the Investigator. The dates of the monitoring visits will be recorded by the monitor in a sign-in log to be kept at the site. The Sponsor expects that, during monitoring visits, the Study Coordinator and Investigator will be available, the source documentation will be available, and a suitable environment will be provided for review of study related documents.
11.2 DATA MANAGEMENT

The Sponsor’s Representative will be responsible for the activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and applicable standard operating procedures. A comprehensive Data Management Plan will be developed, including a data management overview, database content, annotated eCRF, list of electronic edit checks /manual consistency checks, medical coding guidelines and SAE reconciliation plan. Study site personnel will be responsible for all database updates following electronically provided data queries. The clinical research associate (CRA) will be responsible for verification of all data. The Investigator will be required to document the data review to ensure the accuracy of the corrected or clarified data by signing the eCRF electronically.

11.3 DATA HANDLING AND RECORD-KEEPING

11.3.1 Case report forms/Electronic data record

As used in this section the term CRF refers to either a paper form, electronic data record or both, depending upon the data collection method(s) selected for this study.

A CRF must be completed for each patient enrolled in the study. Completed CRFs are the sole property of Mylan and may not be made available in any form to third parties without written permission, except for authorized Representatives of Mylan and appropriate RAs.

Investigators hold final responsibility for ensuring all clinical and safety data is collected, recorded and reported in accordance with protocol, Sponsor and regulatory requirements and timeframes and that data is recorded accurately, completely, and legibly. By signing the Investigator’s Agreement, the Investigator agrees to maintain accurate CRFs and source documentation as part of the case histories for all patients who sign an ICF. Any corrections to data entered into the source document and/or CRF must be dated, initialed and explained as necessary, and should be done in a manner that does not obscure the original entry.

Investigational sites will be provided with access to an electronic remote data capture system that has been fully validated and conforms to 21 Code of Federal Regulations Part 11 requirements. Data Management personnel in collaboration with the CRA will train designated investigational staff on the use of the electronic data capture (EDC) system including any study specific details. ECRF completion guidelines including a user manual will be provided to the sites. Investigational staff will not be given access to the EDC system until they have been trained and assessed as competent to use the system.

Designated investigational staff will enter all requested information required by the protocol into the eCRFs within 48 hours of the completion of the patient visit/receipt of assessment data. To ensure data accuracy, eCRF data for individual patient visits should be completed as soon as possible after the visit. Automated data validation software will
check for data discrepancies in the eCRFs and by generating appropriate error messages, allow modification or verification of the entered data by the investigational staff. A CRA will perform data verification and will document this electronically. The Investigator must certify that data are complete and accurate within the system by providing electronic approval of the eCRF pages.

Before the study starts, a list identifying any data to be recorded directly on the eCRFs (i.e., no prior written or electronic record of data) and considered to be source data will be provided.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to the Sponsor or its designee. Laboratory results will be provided to the study site and should be retained with each patient’s source data.

12 ETHICS

12.1 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the 2008 version of the Declaration of Helsinki, the applicable regulations of the countries in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC (see Appendix D for regulation and guidelines).

12.2 PATIENT INFORMATION AND CONSENT

According to the Declaration of Helsinki and ICH GCP, patients must provide their written informed consent prior to randomization and before any protocol-specified procedures are performed. Patients must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each patient should be made aware by the Investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the EC. Ample opportunity must be given to the patients, their relatives, or, if necessary, their legal representatives, to inquire about details of the study.

Patient information and the ICF must be in a language fully comprehensible to the prospective patient. The written information must be provided to the patient to give her sufficient time to understand the information and to prepare questions before being asked for her consent. The Investigator must confirm that the text was understood by the patient. The patient will then signs and dates the EC-approved consent form, indicating that she has given her consent to participate in the study. The signature confirms the consent is based on information that has been understood. The form will also be signed.
by the Investigator obtaining the consent and annotated with the study patient number. Each patient’s signed ICF must be kept on file by the Investigator for possible inspection by RAs, the Sponsor or its Representatives. Collection of informed consent has to be documented on the eCRF.

Furthermore, the patient will be informed that if she wishes to drop-out or withdraw (see Section 9.1) at any time during the study, this will not have any negative consequences to further treatment at the investigational site. Patients may be withdrawn by the Investigator if any change related to safety or ethics precludes further participation in the study. Patients will be asked to agree to a final assessment in the event of early termination of the study.

Patients will be informed that data from their case may be stored in a computer without inclusion of their name and such data will not be revealed to any unauthorized third party. Data will be reviewed by the CRA, an independent auditor, and possibly by representatives of RAs or ECs. The terms of the local data protection legislation will be applied as appropriate.

12.3 APPROVAL BY INDEPENDENT ETHICS COMMITTEE/INDEPENDENT REVIEW BOARD

A valid IEC/IRB and relevant RA must review and approve this protocol before study initiation. Written notification of approval will include the date of the committee’s approval and the chairperson’s signature. This written approval must consist of a completed EC Approval Form or written documentation from the IEC/IRB containing the same information.

Until written and dated approval/favorable opinion by the IRB/IEC and RA of the protocol, consent form, patient recruitment materials/process (e.g., advertisements), and any other written information to be provided to the patient has been received by the Investigator, no patient may undergo any procedure solely for determining eligibility for this study.

The Principal Investigator should also provide the IRB/IEC with a copy of the IB or product labeling, information to be provided to the patients, reports, updates, and other information (e.g., Safety Updates, Amendments) as required by regulations.

Protocol amendments must also be reviewed and approved (if applicable) by the EC/RA and will not be implemented by the Investigator without written approval by the Sponsor and IRB/IEC/RA, unless required to remove an immediate hazard from a patient. In such case, the written protocol deviation will be immediately reported to both Sponsor and IRB by the Principal Investigator. This written approval will consist of a completed EC Approval Form or written documentation from the EC containing the same information.
13 STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, periodic monitoring visits, and data management.

13.1 SPONSOR’S AND INVESTIGATOR’S RESPONSIBILITIES

13.1.1 Sponsor’s responsibilities

The Sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 12). The Sponsor reserves the right to withdraw a patient from the study (Section 9.1), to terminate participation of a study site at any time (Section 13.6), and/or to discontinue the study (Section 13.6.2).

The Sponsor agrees to provide the Investigator with sufficient study treatment and study-related material as well as reasonable support to permit the Investigator to conduct the study according to the study protocol.

13.1.2 Investigator’s responsibilities

By signing the Investigator’s Agreement (Appendix C), the Investigator indicates that she/he has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The Investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent RAs, including and in accordance with the April 1996 ICH Guidance for Industry E6 GCP and in agreement with the Declaration of Helsinki. While delegation of certain aspects of the study to Sub-Investigators and Study Coordinators is appropriate, the Investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The Investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., Sub-Investigators and Study Coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, the study treatments, and their specific duties within the context of the study. Investigators are responsible for providing the Sponsor with documentation of the qualifications, GCP training and research experience for themselves and their staff, as required by the Sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The Investigator agrees, by written consent to this protocol, to cooperate fully
with compliance checks by allowing access to all study documentation by authorized individuals.

13.2 SITE INITIATION

Study personnel may not screen or enroll patients into the study until they have received notification from the Sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation and shipment of study treatment to the site until all essential documents listed in ICH GCP guideline, Section 8.2 (Before the Clinical Phase of the Trial Commences) have been submitted to and approved by the Sponsor or its designee.

13.3 SCREENING FAILURES

Patients who fail the inclusion or meet the exclusion criteria may be retested for the study. Patients may only be retested once, within 42 days of the original screening visit. Activities associated with tumor burden (i.e., imaging procedures) and laboratory tests must be repeated and be within 28 days before randomization. HER2 and ECHO/MUGA should be repeated only if these were reasons for screening failure. If a patient is eligible to enter the study after having previously failed screening, the patient will be assigned a new patient identification number.

13.4 STUDY DOCUMENTS

All documentation and material provided by the Sponsor for this study prior to study initiation are to be retained in a secure location and treated as confidential material.

13.4.1 Good clinical practice documents

The required GCP documents are listed below:

- Signed (original and dated) FDA Form 1572.
- Signed original and dated protocol (i.e., Investigator’s Agreement).
- Current curricula vitae (CV) of all Investigators and Sub-Investigators (CV must be provided for each individual listed on FDA Form 1572).
- Financial disclosure for each individual listed on the 1572.
- Assurance of an IRB/IEC, which complies with requirements set forth in Title 21 Part 56 of the Code of Federal Regulations, will be responsible for the approval of the clinical study.
- Written notification (copy) to the Investigator from the IRB/IEC approving the protocol. The written notification is to be signed by the chairman or authorized designee and must identify the protocol. In cases where an IRB member has a known conflict of interest, abstention of that individual voting should be documented.
• IRB/IEC approved instrument of informed consent (copy) and any other adjunctive materials to be used in the study, including IRB approval of these items.

• Name and address of the laboratories.

• List of laboratory reference ranges, and if available, a quality certificate.

• Signature Log/Delegation of Study-related Duties.

• Any other relevant GCP documents.

Copies of the Investigator’s GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the IB, eCRF completion guidelines, copies of regulatory references, copies of EC correspondence, and study treatment accountability records, should also be retained as part of the Investigator’s GCP documents. It is the Investigator’s responsibility to ensure that copies of all required GCP documents/records are adequate, and accurate as specified in Essential Documents for the Conduct of Clinical Trial (E6, Section 8 of the ICH Guideline for GCP) to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories: (1) Investigator’s study files and (2) patient clinical source documents.

13.4.2 Source documents

All information recorded in the eCRF must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to: hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to the Sponsor or its designee. Laboratory results will be provided to the study site and should be retained with each patient’s source data.

13.5 AUDITS AND INSPECTIONS

The Sponsor or designee, FDA, and any other regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with Federal regulations. The Investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection. An audit may also be conducted by a representative of the Sponsor.

13.6 STUDY TERMINATION

The study may be terminated at the Sponsor’s discretion at any time and for any reason.

The DSMB may recommend discontinuation of the study if they find evidence of unacceptable risk to patients.
13.6.1 End of study

The end of this study is defined as the date of the last visit of the last patient participating in the study (last patient out or last patient last visit). Within 90 days of the end of the clinical study, the Sponsor or designee will notify the ECs and RAs that the study has ended, as required according to national laws and regulations.

13.6.2 Premature study termination

The study may be terminated prematurely for any reason and at any time by ECs, RAs or the Sponsor upon consultation with the steering committee, DSMB, or the coordinating Investigator. A decision to prematurely terminate the study is binding on all Investigators.

Within 15 days of premature termination of a clinical study, the Sponsor or designee will notify the ECs and RAs about the premature termination as required according to national laws and regulations. The Sponsor or designee must clearly explain the reasons for premature termination.

If the study is terminated prematurely, all Investigators have to inform their patients and take care of appropriate follow-up and further treatment of the patients to ensure protection of the patient’s interests. Study sites may be asked to have all patients currently participating in the study complete all of the assessments for the Early Termination Visit.

13.7 STUDY SITE CLOSURE

At the end of the study, all study sites will be closed. The Sponsor may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Non-compliance with the protocol or applicable regulations and guidelines.
- Inadequate patient enrolment.

13.7.1 Record retention

The Investigator agrees to retain study related records, including: the identity of all participants, all signed informed consent documents, source documents, CRFs, safety reporting documents, records of study drug disposition, documentation of relevant communications (e.g., letters, meeting minutes, telephone, and email contacts).

Records must be retained in accordance with the ICH, local law and/or regulations, or as specified in the Clinical Study Agreement, whichever is longer. Essential documents should be retained until at least 2 years after notification by the Sponsor that investigations have been discontinued or 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. These documents should be retained for a longer period; however if required by the applicable regulatory requirements or by an agreement with
Mylan or designee. In addition, an Investigator shall arrange for the retention of the patient identification codes for at least 15 years after completion of discontinuation of the study. Mylan will notify Investigators in writing when these documents no longer need to be retained. The Investigator must notify Mylan prior to destroying any clinical study records.

If the Investigator is unable to retain study records for the required period (e.g., relocation or retirement) Mylan must be prospectively informed and approve record transfer to a designee, such as a Sub-Investigator, other institution or third party. The Investigator must also obtain Mylan written approval before disposing of any study records.

13.7.1.1 Sample retention

Samples may be retained for purposes related to this research. The samples will be stored until the Sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalyzed. Serum samples may be reanalyzed for immunogenicity and PopPK, while pathohistological samples may be analyzed for HER2 expression and HER2 receptor downstream signaling.

Samples may be stored until 2 years following the last marketing authorization approval in an ICH region. In addition, identifiable samples can be destroyed at any time at the request of the patient.

13.8 CHANGES TO THE PROTOCOL

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of the Sponsor. The protocol amendment must be signed by the Investigator and approved by the EC and relevant RA before it can be implemented, except when necessary to eliminate immediate hazards to the patients.

13.9 FINAL CLINICAL STUDY REPORT

The Sponsor will retain ownership of the data.

The final CSR will be written within 1 year of completion of clinical Part 1 of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR or synopsis will be submitted to the EC and RAs, as required.

Part 1 of the study will result in the main CSR (basis for MAA).

Part 2 of the study will result in an addendum to the main CSR.

Both formats follow ICH guidance.
14 PUBLICATION OF STUDY RESULTS

Information generated by the study is the property of the Sponsor Mylan. Publication or other public presentation of data resulting from this study requires prior review and written approval of Mylan.

Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was prematurely terminated.

14.1 COMMUNICATION OF STUDY RESULTS

This trial will be registered on registry(s) within countries where the study is performed, in accordance with country regulations.

14.2 PUBLICATIONS BY INVESTIGATORS

For all publications relating to the study, Institutions will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

All information concerning the study treatments, Sponsor’s operations, patient applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by the Sponsor or designee to the Investigator and not previously published, is considered confidential and remains the sole property of the Sponsor. Electronic CRFs also remain the property of the Sponsor. The Investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the Sponsor.

The information developed in this study will be used by the Sponsor in connection with the continued development of Hercules and thus may be disclosed as required to other Clinical Investigators or government Regulatory Agencies.

Data from individual study sites must not be published separately. It is agreed that the results of the study will not be submitted for abstract, presentation, poster exhibition or publication by the Investigator until the Sponsor has reviewed and commented on the presentation or manuscript for publication. Abstracts, manuscripts, and presentation materials should be provided to Mylan for review and approval at least 30 days prior to the relevant submission deadline.
15 REFERENCE LIST


22. Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab


16 APPENDICES

Appendix A    TUMOR ASSESSMENT ACCORDING TO RECIST CRITERIA VERSION 1.1 (EISENHAUER 2009)

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement to be recorded) as ≥10 mm with CT or MRI scan (using a slice thickness no greater than 5 mm), ≥10 mm calliper measurement by clinical examination, or ≥20 mm by chest x-ray. All tumor measurements must be recorded in millimetres (or decimal fractions of centimetres).

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT or MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Ultrasound: Ultrasound should not be used to assess tumor lesions. The same holds true for endoscopy or laparoscopy.

Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm), are considered non-measurable disease. Bone lesions, CNS and leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses, skin and cystic lesions are all non-measurable.

Clinical lesions: Clinical lesions will only be considered when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Skin and palpable lesions are to be assessed as non-measurable non-target disease.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as reference by which to characterize the objective tumor response.
Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

Stable Disease (SD): Neither sufficient nor shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-complete Response/Non-Progressive Disease: Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Substantial, unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and
confirmation criteria based on assessment every 6 weeks (Table 16-2). The overall response for all combination of tumor responses (target and non-target lesions) with and without appearance of new lesion is given in Table 16-1.

**Table 16-1 Overall Responses for Target and Non-Target Lesions With and Without the Appearance of New Lesions**

<table>
<thead>
<tr>
<th>Target lesions</th>
<th>Non-target lesions</th>
<th>New lesions</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>no</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>non-CR/non-PD</td>
<td>no</td>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
<td>NE</td>
<td>no</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>non-PD or not all evaluated</td>
<td>no</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>non-PD or not all evaluated</td>
<td>no</td>
<td>SD</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>Non-PD</td>
<td>no</td>
<td>NE</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>yes or no</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>yes or no</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

**Table 16-2 Best Overall Response**

<table>
<thead>
<tr>
<th>Overall response First time point</th>
<th>Overall response Subsequent time point</th>
<th>BEST overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>PR</td>
<td>SD, PD or PRa</td>
</tr>
<tr>
<td>CR</td>
<td>SD</td>
<td>SD provided minimum criteria for SD duration met; otherwise, PD</td>
</tr>
<tr>
<td>CR</td>
<td>PD</td>
<td>SD provided minimum criteria for SD duration met; otherwise, PD</td>
</tr>
<tr>
<td>CR</td>
<td>NE</td>
<td>SD provided minimum criteria for SD duration met; otherwise, NE</td>
</tr>
<tr>
<td>PR</td>
<td>CR</td>
<td>PR or CR</td>
</tr>
<tr>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>PR</td>
<td>PD</td>
<td>SD provided minimum criteria for SD duration met; otherwise, PD</td>
</tr>
<tr>
<td>PR</td>
<td>NE</td>
<td>SD provided minimum criteria for SD duration met; otherwise, NE</td>
</tr>
<tr>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

*a* If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met, i.e., 6 weeks. However, sometimes ‘CR’ may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.
Appendix B  ADDRESS LIST

1. Sponsor

<table>
<thead>
<tr>
<th>Name:</th>
<th>Mylan GmbH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>Thurgauerstrasse 40</td>
</tr>
<tr>
<td></td>
<td>8050 Zurich, Switzerland</td>
</tr>
<tr>
<td>Phone:</td>
<td>+41 44 308 7543</td>
</tr>
<tr>
<td>Fax:</td>
<td>+41 44 308 75 20</td>
</tr>
</tbody>
</table>

2. Clinical Research Organization

<table>
<thead>
<tr>
<th>Name:</th>
<th>INC Research Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>Raleigh, North Carolina</td>
</tr>
<tr>
<td></td>
<td>3201 Beechleaf Court</td>
</tr>
<tr>
<td></td>
<td>Suite 600</td>
</tr>
<tr>
<td></td>
<td>Raleigh, NC 27604-1547, USA</td>
</tr>
<tr>
<td>Phone:</td>
<td>+1 919 876 9300</td>
</tr>
<tr>
<td>Fax:</td>
<td>+1 919 876 9360</td>
</tr>
<tr>
<td>Toll-Free:</td>
<td>+1 866 462 7373</td>
</tr>
</tbody>
</table>

3. Drug Safety

Report Serious Adverse Events and other reportable events to:

**Global Product Safety & Risk Management**
Mylan
Albany Gate, Potters Bar
United Kingdom, EN6 1AG
PV MAIL HUB FOR IMMEDIATE SAFETY REPORTS:
Her3001-PV-Hub@mylan.com

In case an acknowledgment is not received within 24 hours, forward via
Fax: +1-304-285-6409 or Tel: +44 (0)1707 853 000
Appendix C  INVESTIGATOR’S AGREEMENT

<table>
<thead>
<tr>
<th>PROTOCOL NUMBER:</th>
<th>MYL-Her 3001</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTOCOL TITLE:</td>
<td>A Multicenter, Double-blind, Randomized, Parallel-group, Phase III Study of the safety and efficacy of Hercules Plus Taxane Versus Herceptin® Plus Taxane As First Line Therapy in Patients with HER2-Positive Metastatic Breast Cancer</td>
</tr>
<tr>
<td>Version and Date</td>
<td>Amendment 6, Version 9.0, 10 April, 2015</td>
</tr>
</tbody>
</table>

The undersigned acknowledges possession of the protocol and product information and has read the protocol and product information (e.g., Investigator’s Brochure)] on the investigational product (IP) and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IP to selected patients in his/her care, according to the study protocol.

- He/she agrees to use the study material, including IP, only as specified in the protocol. He/she understands that changes cannot be made to the protocol without prior written approval of the sponsor.
- He/she understands that any violation of the protocol may lead to early termination of the study.
- He/she agrees to report to the sponsor within the required time frame any clinical relevant AEs or clinically significant abnormal laboratory values that are serious, whether or not considered related to the administration of IP.
- He/she agrees to comply with sponsor and regulatory requirements for the monitoring and auditing of this study.

In addition, he/she agrees that the study will be carried out in accordance with the revised Declaration of Helsinki and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Investigator:

<table>
<thead>
<tr>
<th>Printed Name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
</tr>
</tbody>
</table>

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Appendix D REGULATIONS AND GOOD CLINICAL PRACTICE GUIDELINES

Regulations

- European Community Directive 2001/20/EC on Clinical Trials
- European Community Directive 2005/28/EC on GCP
- European Community Directive 95/46/EC on storage of personal data

Guidelines