TROIKA

A randomised, double-blind, parallel group, equivalence, multicentre phase III trial to compare the efficacy, safety, and pharmacokinetics of HD201 to Herceptin® in patients with HER2+ early breast cancer

Short title: TROIKA

Sponsor: Prestige BioPharma Pte Ltd

Coordinating investigator: [redacted]

Coordinating study manager: [redacted]

EudraCT no.: 2016-004019-11

Protocol version: Version 3.0 01.10.2018

[redacted]

CONTACT ADDRESSES

Sponsor

Prestige BioPharma Pte Ltd

[redacted]

Sponsor's representative in the European Union

[redacted]

Coordinating investigator and Steering Committee Chair

Chairman: [redacted]

CROs

[redacted]

Data Monitoring Committee [redacted]

Statistics [redacted]

Drug Conditioning & Distribution [redacted]

Protocol committee [redacted]

APPROVAL OF THE PROTOCOL - SPONSOR

Protocol code:	TROIKA
EudraCT number:	2016-004019-11
Title:	A randomised, double-blind, parallel group, equivalence, multicentre phase III trial to compare the efficacy, safety, and pharmacokinetics of HD201 to Herceptin® in patients with HER2+ early breast cancer
Version:	V 3.0. 01.10.2018

Name : [redacted]

[redacted]

Signature

15/OCT/2018

Date (DD/MMM/YYYY)

APPROVAL OF THE PROTOCOL - SPONSOR

Protocol code:	TROIKA
EudraCT number:	2016-004019-11
Title:	A randomised, double-blind, parallel group, equivalence, multicentre phase III trial to compare the efficacy, safety, and pharmacokinetics of HD201 to Herceptin® in patients with HER2+ early breast cancer
Version:	V 3.0. 01.10.2018

Name : [redacted]

[redacted]

Signature

15/Oct/2018

Date (DD/MMM/YYYY)

[redacted]

APPROVAL OF THE PROTOCOL – COORDINATING STUDY MANAGER

Protocol code:	TROIKA
EudraCT number:	2016-004019-11
Title:	A randomised, double-blind, parallel group, equivalence, multicentre phase III trial to compare the efficacy, safety, and pharmacokinetics of HD201 to Herceptin® in patients with HER2+ early breast cancer
Version:	V 3.0. 01.10.2018

Name [redacted]

[redacted]

Signature

12/10/2018

Date (DD/MMM/YYYY)

APPROVAL OF THE PROTOCOL – COORDINATING INVESTIGATOR

Protocol code:	TROIKA
EudraCT number:	2016-004019-11
Title:	A randomised, double-blind, parallel group, equivalence, multicentre phase III trial to compare the efficacy, safety, and pharmacokinetics of HD201 to Herceptin® in patients with HER2+ early breast cancer
Version:	V 3.0. 01.10.2018

Name [redacted]

[redacted]

Signature

11 oct 2018

Date (DD/MMM/YYYY)

APPROVAL OF THE PROTOCOL - STATISTICIAN

Protocol code:	TROIKA
EudraCT number:	2016-004019-11
Title:	A randomised, double-blind, parallel group, equivalence, multicentre phase III trial to compare the efficacy, safety and pharmacokinetics of HD201 to Herceptin® in patients with HER2+ early breast cancer
Version:	V 3.0. 01.10.2018

Name [redacted]

Signature [redacted]

15/OCT/2018

Date (DD/MMM/YYYY)

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled

*"*A randomised, double-blind, parallel group, equivalence, multicentre phase III trial to compare the efficacy, safety and pharmacokinetics of HD201 to Herceptin® in patients with HER2+ early breast cancer", Version 3.0. 01.10.2018.

and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation Tripartite Guideline on Good Clinical Practice, all applicable national regulations as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

I agree to ensure that [redacted]

Investigator name

Date (DD/MMM/YYYY)

Signature

Investigator's institution (if applicable)

SYNOPSIS

Protocol code	TROIKA
Protocol version (Date)	Version 3.0. 01.10.2018
Title	A randomised, double-blind, parallel group, equivalence, multicentre phase III trial to compare the efficacy, safety and pharmacokinetics of HD201 to Herceptin® in patients with HER2+ early breast cancer
EudraCT no.	2016-004019-11
International coordinator	Aesculape CRO Pte Ltd
Sponsor	Prestige BioPharma Pte Ltd
Study design	Randomised, double-blind, parallel group, equivalence, multicentre, international phase III trial. 500 patients with HER2-positive early breast cancer (EBC) will be randomised (1:1) to receive either HD201 in combination with chemotherapy (n=250) or Herceptin® in combination with chemotherapy (n=250). HD201 or Herceptin® will be administered every 3 weeks for 8 cycles. Neoadjuvant chemotherapy will be administered as follows: **Cycles 1-4**: Docetaxel i.v. 75 mg/m² on day 1 of each cycle. **Cycles 5-8**: EC on day 1 of each cycle: • Epirubicin i.v. 75 mg/m² • Cyclophosphamide i.v. 500 mg/m² After administration of the final neoadjuvant study drug dose, surgery will be done within 3-8 weeks followed by an adjuvant treatment period for 10 cycles. After discontinuation of study medication patients will have an End of Treatment (EOT) visit 4 weeks (± 2 days), after the last administration of study medication, followed by a follow-up period of 2 years. Sampling for pharmacokinetics (PK) analysis (determination of C_{trough} values) will be performed in all patients before cycle 5 and cycle 8.
Anticipated start date	Q4 2017
Duration of study	Recruitment phase: ~5 months in Asia, ~6 months in Europe

	Completion of recruitment: Q3 2018 End of study: Q1 2022
Total number of sites	Approximately 130 sites are planned to be initiated in approximately 21 countries.
Study population	Patients with HER2-positive, operable early breast cancer stage II and III
Objectives	
Primary objective	The primary objective of this study is to show equivalence of the total pathological complete response rate (tpCR) in patients treated with HD201 plus chemotherapy to that in patients treated with Herceptin® plus chemotherapy, tpCR will be assessed at the time of surgery after neoadjuvant treatment completion after 24 weeks.
Secondary objectives	• To compare total breast pathological complete response rate (bpCR) between the two arms at the time of surgery. • To compare overall response rate (ORR) between the two treatment arms at the time of surgery. • To compare event-free survival (EFS) between the two treatment arms two years after end of treatment. • To compare overall survival (OS) between the two treatment arms two years after end of treatment. • To compare immunogenicity of HD201 and Herceptin®. • To compare safety and tolerability between the two treatment arms. • To compare the PK trough values of HD201 and Herceptin®.
Planned sample size	It is planned that 500 patients will be randomised to ensure completion of 450 patients (10% drop-out rate assumed). The sample size calculation was based on results from many randomized trials with data for tpCR[11,16,18,22,32]. • The following assumptions are made: the true difference in proportions is 0.00 • the proportion in the reference group is 0.40 (Gianni et al[11]) • the equivalence margin is +/- 0.15 This margin has been motivated by the objective of preserving 60% of the magnitude of the benefit of trastuzumab in terms tpCR, similarly to Stebbing et al[32]
Inclusion criteria	Patients eligible for enrolment in the study must meet all the following inclusion criteria:

1. Able and willing to give written informed consent[1].

2. Females ≥ 18 years of age.

3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) < 2.

4. Known hormone receptor (oestrogen receptor and progesterone receptor) status.

5. HER2 overexpressed as assessed by
   - Immunohistochemistry (IHC) or
   - Fluorescent in site hybridisation (FISH); FISH positive is defined as FISH amplification ratio ≥ 2.0 / number of HER2 gene copies per cell > 2
   - Chromogenic in situ hybridisation (CISH positive)
   - Inform HER2 Dual ISH (DISH positive)
   - Patients with IHC score 3+ or positive FISH/CISH/DISH test
   - Patients with IHC score 2+ must also have a positive FISH/CISH/DISH test.

6. LVEF ≥ 50% or within the normal level of the institution, as assessed by echocardiography or MUGA scan.

7. Life expectancy > 12 weeks.

8. Adequate bone marrow function as evidenced by the following:
   - Absolute neutrophils count ≥ 1,500/μL
   - Haemoglobin ≥ 9 g/dL
   - Platelet count ≥ 100,000/μL

   Maximum 5% deviation is acceptable.

9. Adequate hepatic and renal function as evidenced by the following:
   - Creatinine clearance ≥ 60 mL/min
   - Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
   - AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN

   Maximum 10% deviation is acceptable.

10. Ability to comply with the study protocol.

[1] For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from a legally authorised representative.

	11. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to first dose of study treatment and agree to use effective contraception (intrauterine device, diaphragm, diaphragm with spermicide or a reliable barrier method, e.g. condom, or condom with spermicide) throughout the study period and 7 months after discontinuation of study drug. 12. Non-metastatic, unilateral, newly diagnosed, operable early breast cancer (EBC) of clinical stage II and III including inflammatory breast cancer. o Histologically confirmed primary invasive carcinoma of the breast
Exclusion criteria	Patients meeting any of the following criteria must not be enrolled in the study: 1. Metastatic (stage IV) with exception of supraclavicular nodes. 2. Bilateral Breast Cancer 3. Multicentric breast cancer 4. History of any prior invasive breast carcinoma, except for subjects with a history of ductal carcinoma in situ (DCIS) treated with surgery. 5. History of malignant neoplasms within 5 years prior to randomisation, except for curatively treated carcinoma in situ of uterine cervix, basal cell carcinoma of the skin or squamous cell carcinoma of the skin (malignant neoplasms occurring more than 5 years prior to randomisation are permitted if curatively treated with surgery only). 6. Previous history of radiation therapy, anti-neoplastic immunotherapy, chemotherapy or anti-neoplastic biotherapy (including prior HER2 directed therapy). 7. Major surgery within 2 weeks prior to randomisation 8. Serious cardiac illness that would preclude the use of trastuzumab such as: o history of documented congestive heart failure (CHF) (New York Heart Association, NYHA, class III or greater heart disease)

	○ LVEF < 50% by echocardiography or MUGA scan ○ angina pectoris requiring anti-anginal medication ○ evidence of transmural infarction on electrocardiogram (ECG) ○ uncontrolled hypertension (systolic > 180 mmHg and/or diastolic > 100 mmHg) ○ clinically significant valvular heart disease ○ high-risk uncontrolled arrhythmias. 9. Serious pulmonary illness enough to cause dyspnoea at rest or requiring supplementary oxygen therapy. 10. Known history of active hepatitis B virus (HBV) and active hepatitis C virus (HCV) infection. 11. Known HIV infection by patient declaration. 12. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study. 13. Known hypersensitivity to the IMPs, non-IMPs or any of the ingredients or excipients of the IMPs or non-IMPs. 14. Known hypersensitivity to murine proteins. 15. Pre-existing peripheral sensory or motor neuropathy ≥ grade 2 (as defined by NCI-CTCAE v4.03). 16. Lactating or pregnant woman. A pregnancy test is required for all women of childbearing potential including women who had menopause onset within 2 years prior to randomisation. Women of childbearing potential must agree to use contraceptive methods during the study and for 7 months after the last dose of IMP. 17. Participation in any clinical study or having taken any investigational therapy during the 1-month period immediately preceding administration of the first dose. 18. Patients unwilling to follow the study requirements.
Dosing regimen and treatment	HD201 / Herceptin® (Trastuzumab) during the neoadjuvant period HD201/Herceptin® will be administered as an i.v. loading dose of 8 mg/kg over 90 minutes in Cycle 1, and 6 mg/kg over 60 minutes

then 30 min in subsequent cycles. The dose of HD201/Herceptin® does not need to be recalculated unless the body weight has changed by more than ± 10% from baseline.
In the neoadjuvant setting, HD201/Herceptin® will be administered every 3 weeks until surgery after the end of the 8th cycle, disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever occurs first.

If the patient misses a dose of HD201/Herceptin® by >1 week, a re-loading dose of HD201/Herceptin® (8 mg/kg) or the usual maintenance dose should be given as described in Section 6.3.1.3. Subsequent maintenance HD201/Herceptin® doses of 6 mg/kg will then be continued every 3 weeks.

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy will be administered as follows:

Cycles 1-4: **Docetaxel** 75 mg/m² on day 1 of each 3-weeks cycle via a 1h i.v. infusion.

Cycles 5-8: EC on day 1 of each 3-weeks cycle:

- **Epirubicin** 75 mg/m² to be adminstered between 3-30 minutes via i.v. infusion
- **Cyclophosphamide** 500 mg/m² to be administered between 3-30 minutes via i.v. infusion.

Neoadjuvant chemotherapy is administered immediately after HD201/Herceptin® infusion.

Pre-treatment supportive medication including antiemetics will be given according to institutional practice.

Surgery

After eight cycles of neoadjuvant therapy, surgery will be done within 3-8 weeks of the last dose of HD201 or Herceptin®. Surgery should include breast and axillary nodes dissection (sentinel nodes biopsy is allowed as a possible therapeutic option before and only before the neo-adjuvant therapy in case of clinical node negative status at baseline. When the sentinel node biopsy is negative then a full axillary dissection is not requested after the neo-adjuvant chemotherapy)
After surgery, timeline dependent on the recuperation period post-surgery, patients will enter adjuvant period.

	Adjuvant period After surgery, HD201/Herceptin® will be administered as monotherapy at an i.v. loading dose of 8 mg/kg, then 6 mg/kg (if therapy is missed by >1 week, a re-loading dose of 8 mg/kg or the usual maintenance dose should be given as described in Section 6.3.1.3.) every 3 weeks for 10 cycles (cycles 9-18), disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever occurs first. During the adjuvant period, patients may receive hormonal therapy or radiotherapy or both. Treatment after the adjuvant period will be determined according to the investigator's choice.
Data Monitoring Committee	An independent Data Monitoring Committee (DMC) will be implemented that reviews accumulating data of the clinical trial with respect to any potential safety issues, study progress and critical efficacy endpoints. The DMC will be an independent board consisting of 2-3 physicians with special expertise in breast cancer. The DMC will review only blinded safety and efficacy data of the clinical trial and support the interpretation of clinical trial results. During the trial, the DMC will be provided with SAE and SUSAR listings on a 6-monthly basis.
Primary parameter	tpCR defined as complete absence of cancer cells in the breast and in the axillary lymph nodes (ypT0/is, ypN0) assessed in specimen obtained during surgery.
Secondary parameters	**Efficacy:** • bpCR defined as complete disappearance of cancer cells in the breast (ypT0/is) at the time of surgery. • Overall response rate (ORR) defined as proportion of patients whose best overall response is either complete response (CR) or partial response (PR) as assessed by ultrasound and mammography and clinical examination prior to surgery. • Overall survival (OS) defined as the time from randomisation until death from any cause. • Event-free survival (EFS) defined as the time from randomisation until progression of disease or death from any cause. **Safety and tolerability:** • Safety and tolerability will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events and CTC v4.03

	• Cardiac dysfunction will be monitored by 12-lead ECG and measurement of the LVEF by echocardiography or MUGA scan • Vital signs • Clinical laboratory parameters **Immunogenicity:** Incidence of human trastuzumab antibodies at baseline, before cycle 5 (this sample will only be tested if pre-surgery sample is ADA positive), before surgery, post surgery (before cycle 10), before cycle 14, at end of treatment and one year after completion of trastuzumab therapy. **Pharmacokinetics (and C_{trough}):** Sampling will be performed in all patients. At Cycle 5 (Week 12) and Cycle 8 (Week 21), samples will be taken before administration of treatment (C_{trough}). PK testing will be performed on the first 320 patient samples to obtain values for approximatively 150 in each arm. The remaining samples will be stored for potential future analysis.
Randomisation procedure	Patients will be randomised by IWRS in a 1:1 ratio to HD201 or reference Herceptin®. A list containing the randomization numbers and corresponding treatments will be kept with the IWRS vendor. Patients will be stratified by • Geographical region • Clinical stage: stage II *vs.* III • Oestrogen and progesterone receptor status (positive *vs.* negative)
Statistical considerations	**Efficacy:** *Primary efficacy variable* The primary endpoint will be tpCR, as assessed by local reading. Equivalence will be concluded if the 95% confidence interval on the difference of the two proportions is completely contained within the interval [-15.0;+15.0]. A supportive analysis will be performed, using the same approach, considering tpCR assessed by central reading. A secondary analysis of the primary efficacy variable will be performed by means of a logistic mixed model with treatment, region, stage, oestrogen and progesterone receptor status as fixed factors, and treatment by stage.

	The per-protocol population will be considered primary for the analysis of the primary efficacy variable. *Secondary efficacy variables* All statistical comparisons will be made using two sided tests at the α=0.05 significance level. The intent to treat (ITT)-population will be considered the primary analysis population for the secondary endpoints. Time to event endpoints (OS, EFS) will be analysed using the Kaplan-Meier approach for survival data and Cox regression. **Safety:** All patients who are treated with any amount of study drug will be evaluated for safety. AEs will be summarised by the number and percentage of patients experiencing events by system organ class, preferred term and severity. Changes in vital signs and clinical laboratory measurements will be summarised descriptively by assessment time-point. Other safety variables will be summarised and listed. **Immunogenicity:** Immunogenicity data will be summarised and analysed descriptively for each scheduled protocol assessment time-point. The sample taken at cycle 5 will only be tested if pre-surgery sample is ADA positive, **Pharmacokinetics:** PK data will be summarized and compared for the two arms, based on $C_{trough.}$ Absolute difference value between the two arms and their 90% confidence interval will be provided. Margins of equivalence should be within ± 20%. The evaluation will be performed separately at cycle 5 and cycle 8. PK testing will be performed on the first 320 patient samples to obtain values for approximatively 150 in each arm. The remaining samples will be stored for potential future analysis.
Sample size calculation	It is planned that 500 patients will be randomised to ensure completion of 450 patients (10% drop-out rate assumed). The sample size calculation was based on results from many randomized trials with data for tpCR[11,16,18,22,32]. The following assumptions were used in the sample size calculation: • the true difference in proportions is 0.00 • the proportion in the reference group is 0.40 • the equivalence margin is +/- 0.15

	To have 80% power of showing equivalence data should be available for 224 patients per treatment group. Considering approximately 10% drop-outs or non-evaluable patients a total of 500 patients are to be randomised.
Planned analysis	The planned analysis for the primary endpoint will be done when the last patient has completed surgery. The final analysis will be done when all patients have completed the 2-year follow-up period.

INFORMATION TO BE PROVIDED REGARDING SAES/PREGNANCY

In the case of a serious adverse event (SAE) or pregnancy, the following person must be contacted by or email within 24 hours of knowledge:

Address: [redacted]

Phone: [redacted]

Email: [redacted]

Study procedure	Screening		Neoadjuvant period - Cycle (week) [2]								Before surgery
	-28 days	-7 days	1 (w0)	2 (w3)	3 (w6)	4 (w9)	5 (w12)	6 (w15)	7 (w18)	8 (w21)	
Informed consent	X										
Histologically confirmed EBC	X										
Inclusion & Exclusion Criteria	X										
Demographics	X										
Complete Medical & Surgical History	X										
Physical examination[6]	X		X	X	X	X	X	X	X	X	X
Vital signs[7]	X		X	X	X	X	X	X	X	X	X
Height and weight[8]	X		X	X	X	X	X	X	X	X	X
ECOG performance status	X		X	X	X	X	X	X	X	X	X
Pregnancy test [9]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[10]	X						X				X
LVEF (echocardiography or MUGA)[11]	X						X				X
Haematology[12]		X	X	X	X	X	X	X	X	X	X
Clinical chemistry[13]		X	X	X	X	X	X	X	X	X	X
Immunogenicity sampling[14]	X						X				X
GWAS	X										

[2] Window of ± 2 days will apply to all visits and assessments, except for follow-up survival information collection which will have window of ± 7 days.

[3] Adjuvant therapy for 10 cycles.

[4] At 4 weeks after last administration of study medication for patients completing the treatment period of 12 months and those discontinuing from the study.

[5] After the last administration of study medication patients will be treated according to their physician's discretion. Patients will be followed every 6 months after the EOT visit for an additional period of 2 years or until death, whatever occurs first, to collect data on cardiac safety (ECG/LVEF) and, for patients who underwent surgery, disease status (progression of disease, survival/death, LVEF).

[6] Full physical examination at baseline and EOT. During the study, physical examination should be symptom directed.

[7] Vital signs: blood pressure, pulse rate, body temperature.

[8] Body height at screening only

[9] For women of childbearing potential, pregnancy tests should be performed via serum β-HCG at baseline within 7 days prior to start of treatment. During the treatment period pregnancy tests should be performed according to country-specific requirements. Any positive urine pregnancy test must be confirmed via serum β-HCG. Baseline (and treatment period) pregnancy test results must be available prior to drug infusion.

[10] 12-Lead ECG at screening (within 28 days before start of treatment), before cycle 5, before surgery, before cycles 12 and 16, EOT visit, 6 and 12 months after completion of trastuzumab treatment.

[11] LVEF assessment (echocardiography or MUGA scan) at screening, before cycle 5, before surgery, before cycles 12 and 16, EOT visit and follow-up: 6 and 12 months after completion of trastuzumab (more frequent if necessary). The baseline LVEF assessment should be performed as close as possible to start of treatment (maximum of 28 days prior to start of treatment). Perform LVEF assessment as needed for cardiac safety.

[12] Haematology: haemoglobin, haematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute neutrophil count, absolute lymphocyte count). Laboratory tests must be performed within 2 days prior to each study drug administration, and results must be available prior to each study drug infusion. During the adjuvant period: at Cycles 9, 14 and 18; on other cycles: at the discretion of the investigator. **In general, if baseline laboratory assessments are performed within 7 days prior to study treatment start (day -7 to -1), they will not need to be repeated on day 1 of the start of study treatment.**

[13] Clinical chemistry: Sodium, potassium, BUN/urea, calcium, total protein, albumin, alkaline phosphatase (AP), alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), GGT, total bilirubin, creatinine. Laboratory tests must be performed within 2 days prior to each study drug administration, and results must be available prior to each study drug infusion. During the adjuvant period: at Cycles 9, 14 and 18; on other cycles: at the discretion of the investigator. **In general, if baseline laboratory assessments are performed within 7 days prior to study treatment start (day -7 to -1), they will not need to be repeated on day 1 of the start of study treatment.**

[14] Immunogenicity will be assessed at baseline, before cycle 5 (this sample will only be tested if pre-surgery sample is ADA positive), before surgery, post surgery (before cycle 10), before cycle 14, at EOT visit and one year after completion of trastuzumab treatment. Samples should be taken before administration of study drug. A GWAS sample will be collected, for patients who consented to give GWAS sample, together with the immunogenicity sample at screening (D -28) prior to baseline.

Study procedure	Screening		Neoadjuvant period - Cycle (week) [2]								Before surgery
	-28 days	-7 days	1 (w0)	2 (w3)	3 (w6)	4 (w9)	5 (w12)	6 (w15)	7 (w18)	8 (w21)	
Clinical tumour assessment [15]	X		X	X	X	X	X	X	X	X	X
Tumor assessment by ultrasound and mammography	X										X
HER2 expression (IHC/FISH/CISH/DISH)	X										
Study drug administration			X	X	X	X	X	X	X	X	
PK sample collection [16]							X			X	
CT/MRI scan, Bone scan [17]	X										
Adverse events [18]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X

[15] Clinical tumour size measurement by palpation and by means of a caliper.

[16] Samples for PK analysis will be taken before administration of treatment in cycles 5 and 8.

[17] A bone scan will be performed at screening to rule out bone metastases. Tumour assessment (CT or MRI) will be performed at baseline (day -28 to 0). Scans will be repeated during the treatment period if clinically indicated. **In general, if baseline scans are performed within 6 weeks prior to study treatment start (day -6weeks to -1), they will not need to be repeated on day 1 of the start of study treatment. For scan/imaging results older than 6 weeks, a minor protocol deviation will need to be reported.**

[18] AEs will be recorded from the time of signing the ICF until 7 months after the last administration of IMP. AEs for which the relationship to test drug is not “unrelated” should be followed up until they have returned to baseline status or stabilized.

GLOSSARY OF ABBREVIATIONS

β-HCG	Beta human chorionic gonadotropin
ADA	Anti-drug anitbodies
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT (SGPT)	Alanine aminotransferase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the concentration curve
BSA	Body Surface Area
BUN	Blood urea nitrogen
bpCR	Breast pathological complete response
CISH	Chromogenic in-situ hybridisation
CHF	Congestive heart failure
C_{trough}	Minimum concentration of a drug observed after its administration and just prior to the administration of a subsequent dose
CNS	Central nervous system
CR	Complete response
CRA	Clinical research associate
CRO	Contract research organisation
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
CVAD	Central venous access device
Cy	Cycle
D	Day
DCIS	Ductal carcinoma in situ
DISH	Inform HER2 Dual ISH (DISH positive)
DMC	Data monitoring committee
EBC	Early breast cancer
EC	Epirubicin, cyclophosphamide
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EOT	End of treatment
ESMO	European Society for Medical Oncology
FFPE	Formalin-fixed paraffin embedded
FISH	Fluorescent in-situ hybridisation
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor

GGT	Gamma-glutamyl transferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICH	International Council for Harmonization
IgG1	Immunoglobulin 1
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INR	International normalised ratio
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web response system (IWRS)
Kg	Kilogram
LCIS	Lobular carcinoma in situ
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
m^2	Square metre (body surface area)
mAb	Monoclonal antibody
MBC	Metastatic breast cancer
Mg	Milligram
MGC	Metastatic gastric cancer
Min	Minute
mL	Millilitre
MUGA scan	Multigated acquisition angiogram scan
MRI	Magnetic resonance imaging
Nab	Neutralizing antibodies
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
pCR	Pathological complete response
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per protocol
PR	Partial response
PS	Performance status
RBC	Red blood cell count
RECIST	Response evaluation criteria in solid tumours
RR	Response rate
SAE	Serious adverse event
SD	Stable disease

SmPC	Summary of product characteristics
SADR	Serious adverse drug reaction
SDR	Source data review
SDV	Source data verification
SERM	Selective oestrogen receptor modulator
SUSAR	Suspected unexpected serious adverse reaction
tpCR	Total pathological complete response
TTP	Time to progression
ULN	Upper limit normal
WBC	White blood cell count
W	Week

TABLE OF CONTENTS

1 BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Role of trastuzumab in early breast cancer

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Trastuzumab (Herceptin®) is approved for the treatment of adult patients with HER2-positive metastatic breast cancer (MBC), HER2-early breast cancer (EBC) and HER2-metastatic gastric cancer (MGC).

Overexpression of the HER2 receptor is observed in 20-30% of primary breast cancers[1-4] and is associated with a more aggressive disease and a worse prognosis. Studies have shown that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2[4].

The introduction of trastuzumab (Herceptin®) into the therapeutic armamentarium for HER2-positive breast cancer has dramatically changed the natural history of this disease[1,3,5-7]. However, biotherapies are expensive and not readily available in some countries.

Early breast cancer

The breakthrough of trastuzumab in the treatment of HER2-positive EBC was demonstrated in 2005 with a clear survival outcome achieved by the addition of trastuzumab to chemotherapy[5-7]. Previously, in the early 2000s when the first clinical trial of trastuzumab in the neoadjuvant setting was discontinued prematurely after 34 patients had completed therapy due to an increase of pCR rates in patients receiving trastuzumab plus chemotherapy (pCR: 66.7%) compared to patients receiving chemotherapy alone (pCR: 25%)[8]. Subsequent studies with a larger number of patients confirmed that the usage of trastuzumab is beneficial for patients with HER2-positive EBC[9,10] in terms of survival outcomes[11]. Also, a meta-analysis of 2091 patients by Dawood et al[12] showed that patients with HER2-positive breast cancer who were treated with adjuvant trastuzumab had a better prognosis compared to those without trastuzumab treatment.
Consequently, the current ESMO guideline[13] now recommends (neo)adjuvant treatment consisting of chemotherapy plus trastuzumab for patients with HER2-positive EBC. In most studies, patients were treated with trastuzumab over one year. No additional benefit of a 2-year treatment was demonstrated in the HERA trial[14]. In the PHARE trial[15], non-inferiority of 6 months of trastuzumab compared to 12 months of trastuzumab could not be established, therefore a duration of 12 months of adjuvant trastuzumab remains standard of care.
Neoadjuvant strategies including trastuzumab followed with adjuvant trastuzumab to complete one year of exposure have been providing the same magnitude of survival benefit with higher rate of breast preservation and interestingly a tumour histological response assessment[11,16,17]. A relationship between pCR and survival endpoints was established by a large meta-

analysis[18]. This relationship has suggested the possible use of pCR as an early indicator of efficacy of neoadjuvant regimen. In the neoadjuvant setting, dual anti-HER2 blockade plus chemotherapy (trastuzumab plus lapatinib or pertuzumab) has led to an improvement in pCR rates compared to chemotherapy plus only one anti-HER2 agent[19,20]. However, long-term outcomes for the combination of trastuzumab and lapatinib were not improved, and such a treatment is not recommended by the ESMO guideline[13].
On the other hand, the magnitude of improvement observed with the addition of neoadjuvant pertuzumab allowed an approval for routine use in Europe as well as in the US[20,21]. Nonetheless, currently, the addition of pertuzumab in neo-adjuvant setting is not reimbursed everywhere and this strategy remains a possible therapeutic option as well as the addition of pertuzumab in adjuvant as assessed by Aphinity trial[34]. The neoadjuvant treatment with early pCR assessment might be an optimal setting to compare two anti - HER2 targeted agents or Herceptin® with the candidate biosimilar HD201.
The choice of neoadjuvant chemotherapy need to be considered with cautious to warrant the optimal activity without safety concerns. In the HannaH study, to compare intravenous and subcutaneous trastuzumab the association docetaxel followed by anthracycline containing regimen was used concomitantly administered with trastuzumab[22,23]. The results did not show significant safety concerns and led to subcutaneous trastuzumab approval. The randomized phase III trial (Z1041) evaluated the effect of the timing of trastuzumab administration with anthracycline and taxane neoadjuvant chemotherapy[24]. Although the study did not demonstrate added benefit with concomitant administration of anthracycline and trastuzumab, there were no additional safety concerns. Furthermore, a dose of docetaxel 75 mg/m^2 was used in several studies to increase tolerability. Then the regimen including 4 cycles of docetaxel followed by 4 cycles of anthracycline containing chemotherapy with the concurrent administration of trastuzumab might be considered as a possible option of standard of care for neo-adjuvant treatment in HER2-positive breast cancer[22,24].

1.1.2 Background information on HD201

HD201 was developed as a biosimilar of trastuzumab (Herceptin®) by Hanwha Corporation, Korea and the development is being continued by Prestige BioPharma Pte Ltd, Singapore.

The pharmaceutical presentation and posology of HD201 is the same as for the approved product Herceptin® 150mg powder for concentrate for solution for infusion.

HD201 is a humanised monoclonal antibody for the treatment of HER2-positive early and metastatic breast cancer (EBC and MBC), and metastatic gastric cancer (MGC). The antibody is directed against the extracellular domain of HER2. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, HD201 inhibits the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). *In-vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

HD201 antibody is produced by Chinese Hamster Ovary (CHO) cell suspension culture and purified by various filtration, hydrophobic interaction, and ion exchange chromatography steps that include specific viral inactivation and removal procedures.

Quality development

The development of a biosimilar medicine involves stepwise comparability exercise starting with the comparison of the quality characteristics of the biosimilar products. Hanwha Chemical, the earlier sponsor, had undertaken head-to-head characterisation studies to compare the quality attributes of HD201 to Herceptin®.

These studies demonstrated that the physiochemical and biological activity characteristics of HD201 are comparable to Herceptin®.

Non-clinical development

A series of *in-vitro* PD studies have shown that HD201 and Herceptin® have comparable biological activity. *In-vivo* non-clinical PD, PK, and tissue cross reactivity studies have been conducted.

Further information can be found in the HD201 Investigator's Brochure.

Clinical development

The earlier sponsor, Hanwha Chemical, has conducted a phase I PK study for HD201 from 21.11.2012 to 01.02.2014 (EudraCT no. 2012-000805-56): "A phase I, double-blind, randomised, parallel group study to demonstrate the equivalent pharmacokinetic properties of a single intravenous dose of HD201 and Herceptin in healthy male subjects." In this study, 73 healthy male volunteers were enrolled (37 in the HD201 group and 36 in the Herceptin® group).

The PK of trastuzumab was investigated following a single 90minute IV infusions of HD201 and Herceptin® at 6 mg/kg body weight over a period of 84 days. The overall and peak systemic exposure to trastuzumab was equivalent in both treatment arms. There were no clinically relevant findings associated with vital signs, ECGs, echocardiograms, or laboratory tests. Overall, HD201 was safe and well tolerated.

Further information can be found in the HD201 Investigator's Brochure.

1.2 Study rationale

Trastuzumab has become a key component in the care of patients with HER2 positive breast cancer. However, the high costs of Herceptin® therapy is a burden for health care systems and in many countries, patients only have limited access to therapy with biologics due to the high costs of therapy[25,26]. For these reasons, less expensive alternatives to Herceptin® are sought. This goal may be achieved, at least partly, by the introduction of new biosimilars.

Biosimilars are usually cheaper than their reference products and may therefore broaden the access to a drug[27].
In the TROIKA study, the proposed biosimilar HD201 will be compared to its reference product Herceptin®. The aim of the study is to demonstrate equivalence of HD201 and Herceptin® in terms of efficacy, safety, and pharmacokinetics.

According to the Guideline on similar biological medicinal products (CHMP/437/04 Rev1, 23.10.2014) it is acceptable with appropriate scientific justification to extrapolate the other indications of the reference product if biosimilarity has been demonstrated in one indication. Thereupon it was chosen to establish biosimilarity of HD201 to Herceptin® in patients with EBC.

The advantage of studies with EBC over studies with MBC is that they avoid re-exposition to trastuzumab. Therefore, patients are not resistant to trastuzumab and the risk of immunogenicity is reduced, this is a more homogeneous population with less confounding factors including prior exposure to trastuzumab. This is in line with the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010, 30.05.2012) that states that it “may be advisable not to include patients previously treated with the reference mAB, where possible, or to pre-specify analysis for patients previously treated (in order to explore if pre-treatment impacts immunogenicity), as previous treatment could have resulted in an anti-drug antibody response that could hamper interpretation of the safety data and thus also decrease sensitivity for detecting differences”.

These days, (neo)adjuvant trastuzumab is considered standard therapy in patients with HER2 positive breast cancer[13].

Total pathological complete response rate (tpCR) at the time of surgery was chosen as the primary endpoint of the study. According to the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010, 30.05.2012) classical survival endpoints such as progression free survival (PFS) and overall survival (OS) are not the first choice when evaluating the comparability of a biosimilar mAb to a reference mAb as they may be influenced by factors such as tumour burden, previous lines of therapy, subsequent lines of therapy (in case of OS), underlying clinical conditions etc. Against this, response rates including pCR can detect differences in the activity of the products being compared. Furthermore, pCR is assumed to correlate with survival in patients with locally advanced BC and is therefore an accepted endpoint in clinical trials with EBC[28].

Altogether, the aim of the comparability study is not to demonstrate patient benefit *per se*, which has already been established by the reference product, but to demonstrate comparable efficacy and safety of the proposed biosimilar compared to the reference product.

2 OBJECTIVES OF THE STUDY

2.1 Primary objectives

The primary objective of this study is to compare the total pathological complete response rate (tpCR) in patients treated with HD201 plus chemotherapy to that in patients treated with Herceptin® plus chemotherapy. tpCR will be assessed at the time of surgery after 8 cycles of neoadjuvant treatment completion.

2.2 Secondary objectives

- To compare total breast pathological complete response rate (bpCR) between the two arms at the time of surgery.
- To compare overall response rate (ORR) between the two treatment arms at the time of surgery.
- To compare event-free survival (EFS) between the two treatment arms two years after end of treatment.
- To compare overall survival (OS) between the two treatment arms two years after end of treatment.
- To compare immunogenicity of HD201 and Herceptin®.
- To compare safety and tolerability between the two treatment arms.
- To compare the PK trough values of HD201 and Herceptin®.

3 INVESTIGATIONAL PLAN

3.1 Overview of study design and dosing regimen

This is a randomised, double-blind, parallel group, equivalence, multicentre, international phase III trial. Patients who have histologically confirmed and newly diagnosed clinical stage II-III (as classified according to the AJCC, Breast Cancer Staging, 8th edition[29]), operable, HER2-positive adenocarcinoma of the breast are eligible for the study.

500 patients will be randomised in a 1:1 ratio to one of two treatment arms:

Arm A:

- HD201 (Trastuzumab-biosimilar):
  - 8 mg/kg i.v. loading dose over 90 minutes in Cycle 1,
  - followed by 6 mg/kg IV every 3 weeks over 60 minutes then 30 minutes for subsequent cycles (Cycles 2-8),
  - followed by surgery,
  - 8 mg/kg i.v. loading dose over 90 minutes in Cycle 9
  - followed by adjuvant HD201 6 mg/kg over 30 minutes for subsequent 9 cycles (Cycles 10-18).

- Neoadjuvant chemotherapy:
  - Cycles 1-4: **Docetaxel** 75 mg/m² on day 1 of each 3-weeks cycle via a 1h i.v. infusion
  - Cycles 5-8: EC on day 1 of each 3-weeks cycle:
    - **Epirubicin** 75 mg/m² to be administered between 3-30 minutes via i.v. infusion
    - **Cyclophosphamide** 500 mg/m² to be administered between 3-30 minutes via i.v. infusion

Arm B:

- Herceptin® (Trastuzumab):
  - 8 mg/kg i.v. loading dose over 90 minutes in Cycle 1,
  - followed by 6 mg/kg IV every 3 weeks over 60 min then 30 minutes for subsequent cycles (Cycles 2-8),
  - followed by surgery,
  - 8 mg/kg i.v. loading dose over 90 minutes in Cycle 9
  - followed by adjuvant Herceptin® 6 mg/kg over 30 minutes for subsequent 9 cycles (Cycles 10-18).

- Neoadjuvant chemotherapy:
  - Cycles 1-4: **Docetaxel** 75 mg/m² on day 1 of each 3-weeks cycle via a 1h i.v. infusion
  - Cycles 5-8: EC on day 1 of each 3-weeks cycle:

- **Epirubicin** 75 mg/m² to be administered between 3-30 minutes via i.v. infusion
- **Cyclophosphamide** 500 mg/m² to be administered between 3-30 minutes via i.v. infusion

Neoadjuvant period

In the neoadjuvant setting, HD201/Herceptin® will be administered every 3 weeks until the end of Cycle 8, disease progression, unacceptable toxicity, non-compliance, or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever occurs first.

The dose of HD201/Herceptin® does not need to be recalculated unless the body weight has changed by more than ±10% from baseline.

If a patient misses a dose of HD201/Herceptin® by >1 week, a re-loading dose of HD201/Herceptin® (8 mg/kg) or the usual maintenance dose should be given as described in Section 6.3.1.3. Subsequent maintenance HD201/Herceptin® doses of 6 mg/kg will then be continued every 3 weeks.

Neoadjuvant chemotherapy is administered immediately after HD201/Herceptin® infusion.

Pre-treatment supportive medication including antiemetics will be given according to institutional practice.

Surgery

After eight cycles of neoadjuvant therapy, surgery will be done within 3-8 weeks of the last dose of HD201/Herceptin®. Surgery should include breast and axillary nodes dissection (sentinel nodes biopsy is allowed as a possible therapeutic option before and only before the neo-adjuvant therapy in case of clinical node negative status at baseline. Whether the sentinel node biopsy is negative then a full axillary dissection is not requested after the neo-adjuvant chemotherapy).

After surgery, timeline dependent on the recuperation period post-surgery, patients will enter adjuvant period.

Adjuvant period

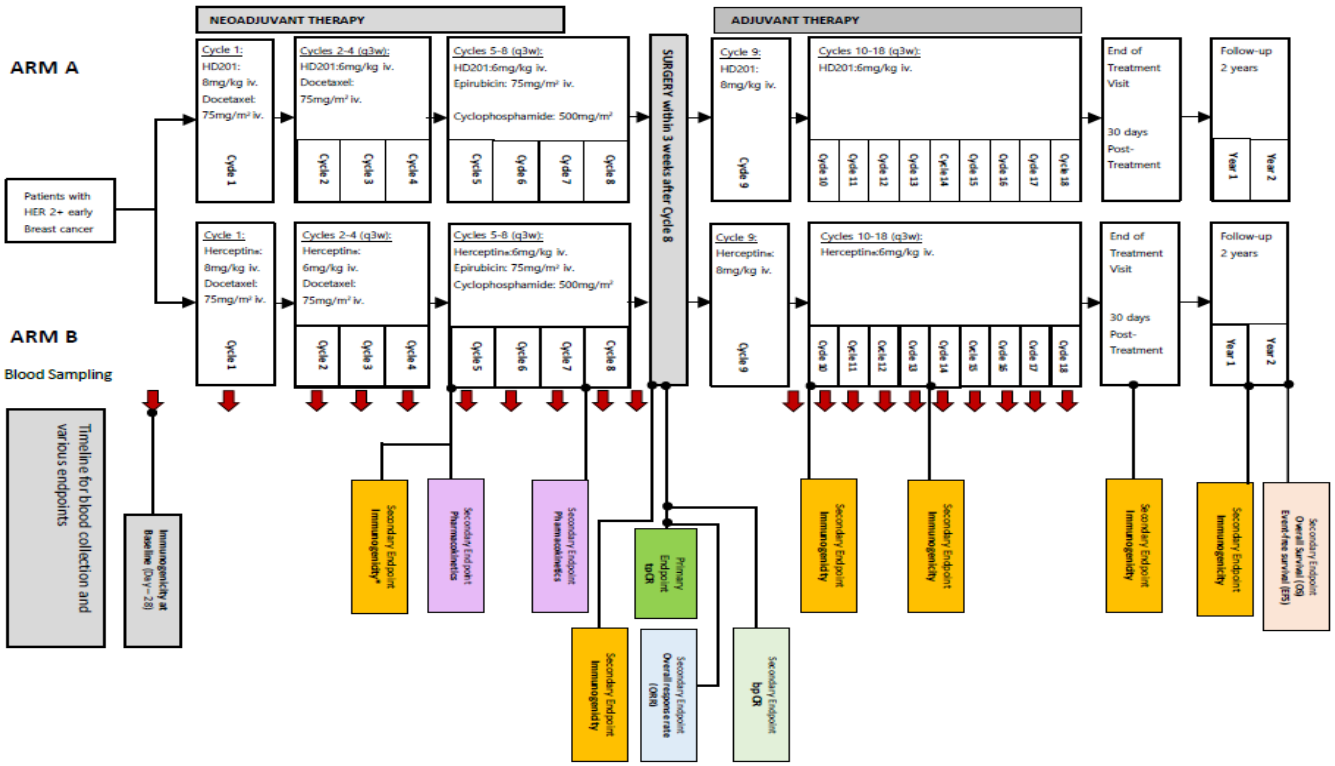
After surgery and depending on patient recuperation period, HD201/Herceptin® will be administered as monotherapy at an i.v. loading dose of 8 mg/kg, then 6 mg/kg (if therapy is missed by >1 week, a re-loading dose of 8 mg/kg or the usual maintenance dose should be given as described in Section 6.3.1.3) every 3 weeks for 10 adjuvant cycles (cycles 9-18), disease progression, unacceptable toxicity, non-compliance, or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever occurs first.

During the adjuvant period, patients may receive hormonal therapy or radiotherapy or both. Treatment after the adjuvant period will be determined according to the investigator's choice.

Efficacy assessment

Total pathological complete response (tpCR) defined as the absence of cancer cells in the breast and axillary lymph nodes (ypT0/is, ypN0) will be evaluated at the time of definitive surgery[30]. tpCR will be assessed both locally and centrally.

A chest and abdomen CT or MRI and bone scan will be done before the patient receives study drug to establish disease stage and rule out metastasis. Additional CTs or MRI and bone scans will only be done if clinically indicated.



*Immunogenicity testing for Cycle 5 will only be tested if pre-surgery sample is ADA positive.

Herceptin®: Sourced from the European Union; q3w: every three weeks

Figure 1:

Study design

3.1.1 Definition of treatment cycle and duration

The duration of one treatment cycle is 3 weeks and each treatment cycle is scheduled from the date of randomisation (Unscheduled treatment cycles may be arranged as described in Section 6.3 & 6.3.1.3).

Patients will be treated with HD201/Herceptin® for a maximum of 18 cycles (8 neo-adjuvant; 10 adjuvant).

3.1.2 End of treatment visit

All patients will undergo an end of treatment (EOT) visit 4 weeks (± 2 days) after the last dose of study medication.

After the last administration of study medication patients will be treated at the discretion of the investigator.

3.1.3 Follow-up phase

After the EOT visit patients will be followed every 6 months for an additional 2 years or until death, whichever occurs first, to collect data on cardiac safety and, for patient who underwent surgery, disease status.

3.1.4 End of study

End of study will be when the last patient has finalised the two-year FU period.

3.2 Assignment of patients to treatment

3.2.1 Randomisation

All patients, who fulfil the inclusion criteria and do not meet any exclusion criteria, will be randomised centrally by IWRS in a ratio of 1:1 to either the HD201 arm or the Herceptin® arm. 500 patients will be randomised. Each patient will be assigned a unique randomization number. A list containing the randomisation numbers and corresponding treatments will be kept with the IWRS vendor.

Patients will be stratified by

- Geographical region
- Clinical stage (stage II *vs.* III)
- Oestrogen and/or progesterone receptor status (positive *vs.* negative)

Patients who were enrolled in this study are not permitted to be randomised in this study again.

3.2.2 Blinding

Patients will be randomised to receive HD201 or Herceptin® in a double-blind fashion such that neither the investigator nor his staff nor the patient nor the sponsor will know which combination is being administered.

HD201 and Herceptin® vials will be presented in identical packaging boxes to ensure blinding of the study medication at the level of packaging. [redacted] However, due to the identical labels affixed on the vials, the pharmacist preparing the infusion bags following reconstitution will not be totally unblinded. Therefore, the pharmacist preparing the infusion bags will only be partially unblinded. The infusion bags will be provided by the pharmacist to the investigator's site, and will be labelled identically, identified by a treatment number, patient number and cycle number, to ensure blinding of the investigator, his staff, and the patient.

The team responsible for study supply and randomisation will not reveal the treatment assignment to the trial team until after database lock for the intermediary analysis (i.e. after the last patient has completed surgery).

The pharmacist will take the necessary measures not to provide access to the study medication packages/vials to the investigator nor his staff. The verification of the drug accountability logs, supplies, including partially used or empty vials and copies of the dispensing forms will be verified by a CRA monitoring the unit.

Individual treatment codes, indicating the treatment assignment in the case of an emergency, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the patient, will be used. Unblinding will only be granted in case of an emergency.

A discussion with the sponsor or the sponsor's medical monitor is recommended before the patient is unblinded. If this is impractical, the investigator should notify the sponsor as soon as possible, but without revealing the treatment assignment of the unblinded patient to the sponsor, unless that information is important for the safety of the patients currently in the study.

The date and reason for unblinding must be recorded in the eCRF.

Patients, investigators, and the sponsor's trial team involved in analysing the trial will remain blinded about the randomised treatment assignments up to database lock for the intermediary analysis (i.e. after the last patient has completed surgery).

3.2.3 Product labelling

The following information will be included on labels in the official language(s) of the country in which the investigational medicinal product is to be used:

(a) Name of the sponsor (Prestige BioPharma Pte Ltd), [redacted];

(b) Name of the substance and its strength or potency, and the name of the comparator
(c) Pharmaceutical dosage form, route of administration (i.v. infusion), quantity of dosage units,
(d) The batch and/or code number to identify the contents and packaging operation;
(e) The trial reference code (EudraCT no.: 2016-004019-11) allowing identification of the trial, site, investigator;
(f) The trial subject identification number/treatment number and the visit number(s);
(g) The name of the investigator
(h) Directions for reconstitution and use (see included leaflet);
(i) “For clinical trial use only”;
(j) Storage conditions: Store between 2–8°C (36°F–46°F), do not freeze, store in the original carton, protect from light;
(k) Expiry date in month/year format

Individual vial labels and labels or the infusion bags will contain the following:
(a) Name of the sponsor (Prestige BioPharma Pte Ltd)
(b) Pharmaceutical dosage form, route of administration (i.v. infusion), quantity of dosage units,
(c) The batch and/or code number to identify the contents and packaging operation;
(d) The trial reference code (EudraCT no.: 2016-004019-11);
(e) The trial subject identification number/treatment number and the cycle number;
(f) Expiry date in month/year format

3.3 Sites

Approximately 130 sites are planned to be initiated in approximately 21 countries.

3.4 Study duration

Start of study:	Q4 2017
Recruitment phase:	~5 months in Asia, ~6 months in Europe
Completion of recruitment:	Q3 2018
Analysis of primary endpoint:	Q1 2019
End of study:	Q1 2022

4 SELECTION OF THE STUDY POPULATION

4.1 Target population

The study population for this trial is women with histologically confirmed and newly diagnosed clinical stage II-III (as classified according to the American Joint Committee on Cancer, Breast Cancer Staging 8th edition[29]), operable, HER2-positive breast adenocarcinoma.

4.2 Inclusion criteria

Patients eligible for enrolment in the study must meet all the following inclusion criteria:

1. Able and willing to give written informed consent[19].

2. Females ≥ 18 years of age.

3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) < 2.

4. Known hormone receptor (oestrogen receptor and progesterone receptor) status.

5. HER2 overexpressed as assessed by
   - Immunohistochemistry (IHC) or
   - Fluorescent in site hybridisation (FISH); FISH positive is defined as FISH amplification ratio ≥ 2.0 / number of HER2 gene copies per cell > 2 or
   - Chromogenetic in situ hybridisation (CISH) positive
   - Inform HER2 Dual ISH (DISH positive)
   - Patients with IHC score 3+ or positive FISH/CISH/DISH test
   - Patients with IHC score 2+ must also have a positive FISH/CISH/DISH test.

6. LVEF ≥ 50% or within the normal level of the institution, as assessed by echocardiography or MUGA scan.

7. Life expectancy > 12 weeks.

8. Adequate bone marrow function as evidenced by the following:

   - Absolute neutrophils count ≥ 1,500/μL
   - Haemoglobin ≥ 9 g/dL
   - Platelet count ≥ 100,000/μL

   Maximum of 5% deviation is acceptable.

[19] For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from a legally authorised representative.

9. Adequate hepatic and renal function as evidenced by the following:

    - Creatinine clearance ≥ 60 mL/min
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
    - AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN

    Maximum of 10% deviation is acceptable.

10. Ability to comply with the study protocol.

11. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to first dose of study treatment and agree to use effective contraception (intrauterine device, diaphragm, diaphragm with spermicide or a reliable barrier method, e.g. condom, condom with spermicide) throughout the study period and 7 months after discontinuation of study drug.

12. Non-metastatic, unilateral, newly diagnosed, operable early breast cancer (EBC) of clinical stage II and III including inflammatory breast cancer. Histologically confirmed primary invasive carcinoma of the breast.

4.3 Exclusion criteria

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

1. Metastatic (stage IV) with exception of supraclavicular nodes.

2. Bilateral breast cancer.

3. Multicentric breast cancer.

4. History of any prior invasive breast carcinoma, except for subjects with a history of ductal carcinoma in situ (DCIS) treated with surgery.

5. History of malignant neoplasms within 5 years prior to randomisation, except for curatively treated carcinoma in situ of uterine cervix, basal cell carcinoma of the skin or squamous cell carcinoma of the skin (malignant neoplasms occurring more than 5 years prior to randomisation are permitted if curatively treated with surgery only).

6. Previous history of radiation therapy, anti-neoplastic immunotherapy, chemotherapy, or anti-neoplastic biotherapy (including prior HER2 directed therapy).

7. Major surgery within 2 weeks prior to randomisation.

8. Serious cardiac illness that would preclude the use of trastuzumab such as:

- history of documented congestive heart failure (CHF) (New York Heart Association, NYHA, class III or greater heart disease)
- LVEF < 50% by echocardiography or MUGA scan
- angina pectoris requiring anti-anginal medication
- evidence of transmural infarction on electrocardiogram (ECG)
- uncontrolled hypertension (systolic > 180 mmHg and/or diastolic > 100 mmHg)
- clinically significant valvular heart disease
- high-risk uncontrolled arrhythmias.

9. Serious pulmonary illness enough to cause dyspnoea at rest or requiring supplementary oxygen therapy.

10. Known history of active hepatitis B virus (HBV) and active hepatitis C virus (HCV) infection.

11. Known HIV infection by patient declaration.

12. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.

13. Known hypersensitivity to the IMPs, non-IMPs or any of the ingredients or excipients of the IMPs or non-IMPs.

14. Known hypersensitivity to murine proteins.

15. Pre-existing peripheral sensory or motor neuropathy ≥ grade 2 (as defined by NCI-CTCAE v4.03).

16. Lactating or pregnant woman. A pregnancy test is required for all women of childbearing potential including women who had menopause onset within 2 years prior to randomisation. Women of childbearing potential must agree to use contraceptive methods during the study and for 7 months after the last dose of IMP.

17. Participation in any clinical study or having taken any investigational therapy during the 1-month period immediately preceding administration of the first dose.

18. Patients unwilling to follow the study requirements.

5 SCHEDULE OF ASSESSMENT AND PROCEDURES

5.1 Study assessments

5.1.1 Tumour assessments

The minimum screening examinations should include:

- CT or MRI scan of the chest and abdomen (including liver, spleen, and adrenals)
- CT or MRI scan of the brain and/or spine where there is clinical suspicion of CNS metastases
- An isotope bone scan at baseline to rule out bone metastases. It should be repeated in the event of clinical suspicion of the appearance of bone lesions.

  The breast tumour should be assessed before and after neoadjuvant treatment by mammography, ultrasound, and clinical assessment.

The diagnosis of a breast cancer progression or recurrence can be made only when the clinical, laboratory, radiological and/or histological findings meet the criteria of “acceptable’ as defined below. Suspicious findings do not constitute criteria for breast cancer recurrence, nor are they an indication to alter protocol therapy.

Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the investigator.

Local recurrence / local progression
Local recurrence is defined as evidence of breast cancer (invasive or in situ) in the ipsilateral breast or skin of the breast after surgery. When local recurrence occurs in the ipsilateral breast parenchyma after conservative surgery it is termed ‘Ipsilateral breast tumour recurrence (IBTR’). Patients who develop clinical evidence of tumour recurrence in the remainder of the ipsilateral breast must have a biopsy of the suspicious lesion to confirm the diagnosis.
Acceptable: Positive histological biopsy.

Local progression is defined as increase of tumour size under treatment (during primary chemotherapy)
Acceptable: Positive histological biopsy, imaging.

Other local recurrence/progression
Defined as appearance of breast cancer in the skin of the chest wall (exclusive of the breast) or chest wall after surgery (recurrence) or during primary chemotherapy (progression).

Regional recurrence / Regional progression
Defined as increase in size or new appearance of tumour in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, following surgery.
Acceptable: Positive histological biopsy.

Contralateral invasive breast cancer
Defined as evidence of invasive breast cancer in the contra lateral breast or chest wall. The diagnosis of contra lateral breast cancer must be confirmed histologically.
Acceptable: Positive histological biopsy.

Distant recurrence/Distant progression
Defined as evidence of tumour in all areas, except for those described in the previous sections.

- Skin, subcutaneous tissue, and lymph nodes (other than local or regional)

Acceptable: Positive histology, aspirate or biopsy, or radiologic evidence of metastatic disease.

- Bone marrow metastasis

Acceptable: Positive histology, biopsy, or MRI scan.

- Lung metastasis

Acceptable: Positive histology or biopsy or radiologic evidence of multiple pulmonary nodules that are judged to be consistent with pulmonary metastases.

Note: If a solitary lung lesion is found and no other lesions are present on lung tomograms, CT scan, or MRI scan, further investigations, such as biopsy, needle aspiration, or PET scan must be performed. Proof of neoplastic pleural effusion must be established by histology or pleural biopsy.

- Skeletal metastasis

Acceptable: CT or MRI evidence of lytic or blastic lesions consistent with bone metastasis, or bone scan that is clearly positive for bone metastases.

Note: If the diagnosis is equivocal by bone scan or radiologic evaluation, a biopsy is strongly recommended. Any positive bone scan in joints or in a recent area of trauma (surgical or otherwise) cannot be used as a criterion for breast cancer recurrence.

- Liver metastasis

Acceptable: an abdominal CT scan, liver scan, ultrasound, or MRI consistent with liver metastases or liver biopsy confirmation of the metastatic disease.

Note: If the radiologic findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans must be obtained to document stability or progression.

- Central nervous system

  Acceptable: Positive CT scan or MRI scan, usually in a patient with neurological symptoms, or biopsy or histology (for a diagnosis of leptomeningeal involvement).

5.1.1.1 Independent review of pathological specimens

One of the supportive endpoints of this trial is the rate of total pathological Complete Response (tpCR) at the time of definite surgery as read by a central laboratory. A minimum of 10 to 15 paraffin blocks from the initial primary tumour bed will be examined by a central laboratory. Detailed instructions will be given once all patients will have undergone surgery and paraffin blocks will be ready for shipment.

5.1.2 Other clinical assessments

5.1.2.1 HER2 overexpression

HER2 overexpression or HER2 gene amplification should be determined by a validated assay. HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of FFPE tumour tissue, HER2 gene amplification should be detected using fluorescence *in situ* hybridisation (FISH) of FFPE tumour tissue.

The recommended scoring system to evaluate IHC staining patterns is as follows:

Score	Staining pattern	HER2 overexpression assessment
0	No staining is observed or membrane staining is observed in <10% of the tumour cells.	Negative
1+	A faint/barely perceptible membrane staining is detected in >10% of the tumour cells. The cells are only stained in part of their membrane.	Negative
2+	A weak to moderate complete membrane staining is detected in >10% is the tumour cells.	Equivocal
3+	Strong complete membrane staining is detected in >10% of the tumour cells.	Positive

The FISH test measures the amount of HER2 gene that is responsible for the overexpression of the HER2 protein. The result of the FISH test will either be negative (normal gene level) or positive. In general, FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2, or if there are more than 2 copies of the HER2 gene per tumour cell if no chromosome 17 control is used.

HER2-positive tumours are defined as either IHC score 3+ or IHC2+/FISH+ or FISH+ or IHC2+/CISH+ or CISH+ or IHC2+/DISH+ or DISH+.

5.1.2.2 ECG assessment

12-Lead ECG at screening (within 28 days before start of treatment), before cycle 5, before surgery, before cycles 12 and 16, EOT visit and during follow-up: at 6 and 12 months after completion of trastuzumab treatment.

5.1.2.3 LVEF assessment

LVEF assessment at screening (within 28 days before start of treatment), before cycle 5, before surgery, before cycles 12 and 16, EOT visit, and during follow-up: at 6 and 12 months after completion of trastuzumab treatment.

All patients must have their LVEF assessed by 2D echocardiography (ECHO) or multi-gated acquisition scan (MUGA scan) as part of the screening procedure and throughout the study. ECHO is the preferred method because it can detect wall-motion abnormalities. LVEF is to be calculated using the modified Simpson method, and must be ≥ 50% at baseline as determined by the local facility before a patient can be enrolled in the study. The investigator must decide which method of LVEF assessment (ECHO or MUGA scan) will be used for each patient at baseline, and the same method and the same institution/facility should be used throughout the study, to the extent possible. The LLN for the LVEF facility will be reported along with the LVEF result.

5.1.2.4 Pharmacokinetic analysis

Sampling will be performed in all patients to determine C_{trough}.

Samples for PK analysis (determination of C_{trough}) will be taken before administration of treatment in cycles 5 and 8.

The samples will be submitted for analysis to the central laboratory.

PK testing will be performed on the first 320 patient samples to obtain values for approximatively 150 in each arm. The remaining samples will be stored for potential future analysis.

5.1.3 Safety assessments

Throughout the treatment period and until 7 months after the last administration of study treatment, patients will be assessed for all adverse events. Common terminology criteria for adverse events (CTCAE v4.03) will be used for grading. If necessary, the patient may be withdrawn from the study treatment.

- **Medical history** including cancer and treatment history will be reviewed and recorded at the screening visit.
- **Concomitant medications** will be documented throughout treatment phase until the EOT visit.
- **Adverse events** (see also Section 7.1): All patients will be closely monitored for adverse events from the time of signing the ICF until 7 months after the last administration of treatment. Adverse events for which the relationship to test drug is not “unrelated” should be followed up until they have returned to baseline status or stabilised.

5.1.4 Laboratory assessments

All local laboratory sample collection and testing will be scheduled as indicated in Table 1. Additional assessments may be performed as clinically indicated or as per local practice. Normal ranges for the local laboratory parameters must be supplied to the study sponsor before the study starts.

The following tests will be performed at a local laboratory:

- **Haematology**: Haemoglobin, haematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute neutrophil count, absolute lymphocyte count).
  Additional tests may be performed per the institution’s standard practice. Testing will be performed at baseline, at least before the start of every chemotherapy cycle, at the End of treatment (EOT) visit, and when clinically indicated.

- **Clinical chemistry:** Sodium, potassium, BUN/urea, calcium, total protein, albumin, alkaline phosphatase (AP), alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), GGT, total bilirubin, creatinine.

Additional tests may be performed per institution's standard practice. Testing will be performed at baseline, at least before the start of every chemotherapy cycle, at the End of treatment (EOT) visit, and when clinically indicated.

- **Pregnancy test**: For women of childbearing potential, pregnancy tests should be performed via serum β-HCG at baseline within 7 days prior to start of treatment. During the treatment period pregnancy tests should be performed according to country-specific requirements. Any positive urine pregnancy test must be confirmed via serum β-HCG. Pregnancy test results must be available prior to the drug infusion.

  Following tests will be performed centrally:

- **Pharmacokinetics and immunogenicity**
  Sampling for pharmacokinetics (PK) analysis (determination of C_{trough} values) will be performed in all patients. Samples for PK analysis should be taken before administration of study drug in cycles 5 and 8.
  PK testing will be performed on the first 320 patient samples to obtain values for approximatively 150 in each arm. The remaining samples will be stored for potential future analysis.

  Immunogenicity will be assessed at baseline, before cycle 5 (this sample will only be tested if pre-surgery sample is ADA positive), before surgery, post surgery (before cycle 10), before cycle 14, at EOT visit and one year after completion of trastuzumab treatment. Samples should be taken before administration of study drug. Detailed sampling procedures are described in the Lab Manual.

- **GWAS**: a genome-wide association study (GWAS). This will focus on associations between single-nucleotide polymorphisms (SNPs) and HER2 + eBC treatment. A case to case GWAS design will be used to identify variants associated with pCR and/or cardiotoxicity related to trastuzumab. One blood sample is taken at baseline in patients who consented to giving a blood sample for GWAS for a centralized analysis.

The relevant laboratory assessments must be available prior to each administration of study treatment for dose modification or delay requirements as specified in Section 6.3. These assessments must be performed within 2 days prior to the administration of study treatment at each cycle.

NOTE: Haematology, clinical chemistry, and serum β-HCG tests are only valid as part of baseline eligibility screening if they have been performed within 7 days of randomisation.

In general, if baseline laboratory assessments are performed 7 days (day -7 to -1) prior to study treatment start, they will not need to be repeated on day 1 of the start of study treatment. Any abnormalities that are discovered during patient assessment should be further investigated where clinically indicated, to ensure that patients are fit to be included in the study and to receive study medication.

5.2 Study procedures

The Schedule of Study Events is displayed in tabular form as **Table 1.**

TABLE 1: FLOW CHART: SCHEDULE OF ASSESSMENTS DURING THE STUDY

Study procedure	Screening		Neoadjuvant period - Cycle (week) [2]								Before surgery	Adjuvant period[3]	EOT[4]	Follow-up[5]
	-28 days	-7 days	1 (w0)	2 (w3)	3 (w6)	4 (w9)	5 (w12)	6 (w15)	7 (w18)	8 (w21)				
Informed consent	X													
Histologically confirmed EBC	X													
Inclusion & Exclusion Criteria	X													
Demographics	X													
Complete Medical & Surgical History	X													
Physical examination[6]	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[7]	X		X	X	X	X	X	X	X	X	X	X	X	X
Height and weight[8]	X		X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X		X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test [9]	X	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG[10]	X						X				X	X	X	X
LVEF (echocardiography or MUGA)[11]	X						X				X	X	X	X

[2] A window of ± 2 days will apply to all visits and assessments, except for follow-up survival information collection which will have a window of ± 7 days.
[3] Adjuvant therapy for 10 cycles.
[4] At 4 weeks after last administration of study medication for patients completing the treatment period of 12 months and those discontinuing from the study.
[5] After the last administration of study medication patients will be treated according to their physician's discretion. Patients will be followed every 6 months after the EOT visit for an additional period of 2 years or until death, whatever occurs first, to collect data on cardiac safety (ECG/LVEF) and, for patients who underwent surgery, disease status (progression of disease, survival/death).
[6] Full physical examination at baseline and EOT. During the study, physical examination should be symptom directed.
[7] Vital signs: blood pressure, pulse rate, body temperature.
[8] Body height at screening only
[9] For women of childbearing potential, pregnancy tests should be performed via serum β-HCG at baseline within 7 days prior to start of treatment. During the treatment period pregnancy tests should be performed according to country-specific requirements. Any positive urine pregnancy test must be confirmed via serum β-HCG. Baseline (and treatment period) pregnancy test results must be available prior to drug infusion.
[10] 12-Lead ECG at screening (within 28 days before start of treatment), before cycle 5, before surgery, before cycles 12 and 16, EOT visit, 6 and 12 months after completion of trastuzumab treatment.
[11] LVEF assessment (echocardiography or MUGA scan) at screening, before cycle 5, before surgery, before cycles 12 and 16, EOT visit and follow-up: 6 and 12 months after completion of trastuzumab (more frequent if necessary). The baseline LVEF assessment should be performed as close as possible to start of treatment (maximum of 28 days prior to start of treatment). Perform LVEF assessment as needed for cardiac safety.

Study procedure	Screening		Neoadjuvant period - Cycle (week) [2]								Before surgery	Adjuvant period[3]	EOT[4]	Follow-up[5]
	-28 days	-7 days	1 (w0)	2 (w3)	3 (w6)	4 (w9)	5 (w12)	6 (w15)	7 (w18)	8 (w21)				
Haematology[12]		X	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry[13]		X	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity sampling[14]	X						X				X	X	X	X
GWAS	X													
Clinical tumour assessment [15]	X		X	X	X	X	X	X	X	X	X			
Tumor assessment by ultrasound and mammography	X										X			
HER2 expression (IHC/FISH/CISH/DISH)	X													
Study drug administration			X	X	X	X	X	X	X	X		X		
PK sample collection [16]							X			X				
CT/MRI scan, Bone scan [17]	X													
Adverse events [18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	

.

[12] Haematology: haemoglobin, haematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (neutrophils). Laboratory tests must be performed within 2 days prior to each study drug administration, and results must be available prior to each study drug infusion. During the adjuvant period: at Cycles 9, 14, and 18; on other cycles: at the discretion of the investigator. **In general, if baseline laboratory assessments are performed within 7 days prior to study treatment start (day -7 to -1), they will not need to be repeated on day 1 of the start of study treatment.**

[13] Clinical chemistry: Sodium, potassium, BUN/urea, calcium, total protein, albumin, alkaline phosphatase (AP), alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), GGT, total bilirubin, creatinine. Laboratory tests must be performed within 2 days prior to each study drug administration, and results must be available prior to each study drug infusion. During the adjuvant period: at Cycles 9, 14, and 18; on other cycles: at the discretion of the investigator. **In general, if baseline laboratory assessments are performed within 7 days prior to study treatment start (day -7 to -1), they will not need to be repeated on day 1 of the start of study treatment.**

[14] Immunogenicity will be assessed at baseline, before cycle 5 (this sample will only be tested if pre-surgery sample is ADA positive), before surgery, post surgery (before cycle 10), before cycle 14, at EOT visit and one year after completion of trastuzumab treatment. Samples should be taken before administration of study drug. A GWAS sample will be collected, for patients who consented to give GWAS sample, together with the immunogenicity sample at screening (D -28) prior to baseline.

[15] Clinical tumour size measurement by palpation and by means of a caliper.

[16] Samples for PK analysis will be taken before administration of treatment in cycles 5 and 8.

[17] A bone scan will be performed at screening to rule out bone metastases. Tumour assessment (CT or MRI) will be performed at baseline (day -28 to 0). Scans will be repeated during the treatment period if clinically indicated. **In general, if baseline scans are performed within 6 weeks prior to study treatment start (day -6weeks to -1), they will not need to be repeated on day 1 of the start of study treatment. For scan/imaging results older than 6 weeks, a minor protocol deviation will need to be reported.**

[18] AEs will be recorded from the time of signing the ICF until 7 months after the last administration of treatment. AEs for which the relationship to test drug is not “unrelated” should be followed up until they have returned to baseline status or stabilised

5.2.1 Screening procedures

All patients will be screened, and screening procedures performed within 28 days prior to start of induction treatment unless specified otherwise below. The following procedures are performed:

Signed written informed consent	Obtained prior to any study-specific assessments. A separate consent will be required for GWAS sampling.
Tumour tissue for HER2 status	Before randomisation into the study, patients must have HER2 positive breast cancer defined as 3+ by IHC or FISH amplification ratio ≥ 2.0 / number of HER2 gene copies per cell > 2 or CISH/DISH positive.
Demographics and medical history	• Age, gender, race • Previous and concurrent relevant diseases • Breast cancer history including tumour characteristics (i.e., hormone receptor status, etc.) • Current symptoms
Inclusion and exclusion criteria	Review of all inclusion and exclusion criteria
Physical examination and vital signs	• Blood pressure, pulse rate, body temperature • Body height and weight • BSA • Physical examination: In the physical examination, particular care should be taken with regard to cardiovascular signs and symptoms.
ECOG Performance Status	Please refer to Appendix 2 (Section 17.2)
Tumour assessment	• Tumour assessment should be performed as specified in Section 5.1.1. A CT or MRI brain scan is to be performed at screening only in patients with signs or symptoms suggesting CNS involvement or other unexplained neurological symptoms, and during the study, if clinically indicated. • Clinical assessment. • Measurement of the primary tumour and regional nodes by bilateral mammography and ultrasound.
Bone scan	To rule out metastases

Cardiac examination	• LVEF assessment: All patients must have their LVEF assessed by 2D echocardiography (ECHO) or multi-gated-acquisition (MUGA) scan as part of the screening procedure. The baseline LVEF assessment should be performed as close as possible to start of treatment (maximum of 28 days prior to start of treatment). LVEF must be ≥ 50% at baseline as determined by the local facility before a patient can be enrolled in the study. • 12-Lead ECG
Adverse events and concomitant medication	Concomitant medication currently used.
Haematolgy, clinical chemistry	Should be performed at a local laboratory within 7 days prior to the first administration of study medication (see Section 5.1.4 for specific tests required).
GWAS	Will be collected at screening (D -28) prior to baseline in patients who consented to give a blood sample for GWAS and submitted to a central laboratory
Pregnancy test	A serum β-HCG test must be performed for all women of childbearing potential, and for all women not meeting the definition of postmenopausal (≥ 24 months of amenorrhea), and who have not undergone surgical sterilisation. Testing should be performed at a local laboratory within 7 days prior to the first administration of study medication. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential (see Section 5.1.4). In case the sampling date for the serum pregnancy test exceeds 7 days before treatment start, a urine test is required for confirmation.
Immunogenicity sample	Should be collected within 28 days to the first administration of study medication. The samples will be submitted to the central laboratory. To be noted that only ADA-positive samples will be tested for Nab.

5.2.2 Neoadjuvant treatment phase

During the neoadjuvant treatment (cycles 1-8) the following assessments are to be performed according to the study flow chart within the allowed visit windows (± 2 days):

Physical examination and vital signs	• Blood pressure, pulse rate, body temperature • Body weight • BSA • Physical examination
ECOG Performance Status	Please refer to Appendix 2 (Section 17.2) Record before administration of study drug
12-Lead ECG	Cycle 5, before administration of study drug. More frequent monitoring may be performed when more frequent LVEF monitoring is performed as needed for cardiac safety.
Tumour assessment	• Tumour assessment should be performed as specified in Section 5.1.1. • Clinical assessment by palpation at each cycle. • Measurement of the primary breast tumour and regional lymph nodes at each cycle. Tumour size will be assessed clinically
LVEF assessment	LVEF assessment must be performed in Cycle 5, before administration of study drug. More frequent LVEF monitoring may be performed as needed for cardiac safety. The same method of LVEF assessment (ECHO or MUGA scan) and the same institution/facility used at baseline should be used throughout the study, to the extent possible. The LLN for the LVEF facility will be reported along with each LVEF result.
Bone scan / MRI	Only if clinically indicated
Adverse events and concomitant medication	Assessed on an ongoing basis
Haematology, clinical chemistry	Will be collected and submitted to a local laboratory within 2 days prior to administration of each study treatment, or when clinically indicated (see Section 5.1.4).
Pregnancy test	At each cycle, according to country-specific requirements. Any positive urine pregnancy test must be

	confirmed via serum β-HCG. Pregnancy test results must be available prior to the drug infusion.
Blood draws for pharmacokinetics (PK)	Samples for PK analysis will be taken before administration of treatment in cycles 5 and 8. Samples will be submitted to the central laboratory. PK testing will be performed on the first 320 patient samples to obtain values for approximatively 150 in each arm. The remaining samples will be stored for potential future analysis.

5.2.3 Before surgery

Surgery will be done within 3-8 weeks after cycle 8. The following assessment will be done approximately 3 weeks after cycle 8, but before surgery:

Physical examination and vital signs	• Blood pressure, pulse rate, body temperature • Body weight • Physical examination
ECOG Performance Status	Please refer to Appendix 2 (Section 17.2)
Pregnancy test	A pregnancy test should be performed according to country-specific requirements. Any positive urine pregnancy test must be confirmed via serum β-HCG.
Tumour assessment	• Tumour assessment should be performed as specified in Section 5.1.1. • Measurement of the primary breast tumour and regional lymph nodes. Tumour size will be measured by ultrasound and mammography and clinically.
12-Lead ECG	
LVEF assessment	
Adverse events and concomitant medication	Assessed on an ongoing basis
Haematology, clinical chemistry	see Section 5.1.4
Immunogenicity sample	A sample for immunogenicity assessment will be taken and submitted to the central laboratory. To be noted that only ADA-positive samples will be tested for Nab. For

	these ADA-positive samples, immunogenicity will be tested on the Cycle 5 sample as well.

5.2.4 Surgery

Surgery should be performed according to procedures decided by the local surgeon who should consider tumour size, breast volume, and patient's attitude.

Whenever possible, in operable and locally advanced non-inflammatory cancer, conservation methods should be preferred. Conservation should consist of a wide resection, with safe free margins.

Conservative surgery is not recommended for inflammatory breast cancer or in the presence of extensive microcalcifications.

Axillary surgery
Axillary lymph node dissection (ALND) is recommended. Lymph node axillary dissection must include the first and second level. Sentinel node biopsy is allowed as a possible therapeutic option in cN0 before neo-adjuvant therapy and 3 to 5 “sentinel nodes” are recommended to minimize the false negative rate. Sentinel node biopsy must be followed by ALND if positive nodes are found. When the sentinel node biopsy is negative a full axillary dissection is not required after the neo-adjuvant chemotherapy.

5.2.5 Adjuvant treatment phase

After surgery and depending on recuperation period required by each patient, HD201/Herceptin® will be administered as adjuvant monotherapy at an i.v. loading dose of 8 mg/kg, then 6 mg/kg (if therapy is missed by >1 week, a re-loading dose of 8 mg/kg or the usual maintenance does as described in Section 6.3.1.3 should be given) every 3 weeks to complete 10 adjuvant cycles (cycles 9-18). The following assessments will be performed within the allowed time window (± 2 days):

Physical examination and vital signs	• Blood pressure, pulse rate, body temperature • Body weight • Physical examination
ECOG Performance Status	Please refer to Appendix 2 (Section 17.2) Record before administration of study drug
12-Lead ECG	Before cycles 12 and 16. More frequent monitoring may be performed when more frequent LVEF monitoring is performed as needed for cardiac safety.
LVEF assessment	LVEF assessments are done before cycle 12 and cycle 16 during the adjuvant period. More frequent LVEF monitoring may be performed as needed for cardiac

	safety. The same method of LVEF assessment (ECHO or MUGA scan) and the same institution/facility used at baseline should be used throughout the study, to the extent possible. The LLN for the LVEF facility will be reported along with each LVEF result.
Bone scan / MRI	Only if clinically indicated
Adverse events and concomitant medication	Assessed on an ongoing basis
Haematology, clinical chemistry	At cycles 9, 14, and 18, and on other cycles at the discretion of the investigator. Samples will be collected and submitted to a local laboratory within 2 days prior to administration of each study treatment, or when clinically indicated (see Section 5.1.4).
Immunogenicity sample	A sample for immunogenicity assessment will be taken post surgery (before cycle 10) and before cycle 14 and submitted to the central laboratory. To be noted that only ADA-positive samples will be tested for Nab.
Pregnancy test	At each cycle during the treatment period pregnancy tests should be performed according to country-specific requirements. Any positive urine pregnancy test must be confirmed via serum β-HCG. Pregnancy test results must be available prior to the drug infusion.

5.2.6 End of treatment

All patients must have an end of treatment (EOT) visit completed 4 weeks (± 2 days) after the last application of study drug, regardless of the reason for treatment stop (regular end of treatment or premature discontinuation).
At the EOT visit the patient will undergo the following assessments:

Physical examination and vital signs	• Blood pressure, pulse rate, body temperature • Body weight • Physical examination
ECOG performance status	Please refer to Appendix 2 (Section 17.2)
12-Lead ECG	For all patients, a 12-lead ECG should be done at the end of treatment visit.

LVEF assessment	For all patients, LVEF assessments should be done within one month after cycle 18. Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 18 weeks, until the LVEF values return to ≥ 50%, or 1 year, whichever comes first.
Haematology, clinical chemistry	Will be collected and submitted to a local laboratory at the EOT visit (see Section 5.1.4).
Adverse Events and Concomitant Medication	Assessed on an ongoing basis Cardiac adverse events occurring up to 12 months after last administration of study medications must be reported irrespective of causal relationship.
Immunogenicity sampling	A sample for immunogenicity assessment will be taken and submitted to the central laboratory. To be noted that only ADA-positive samples will be tested for Nab.

5.2.7 Follow-up

All patients (except if they discontinued from treatment due to withdrawal of consent) will be followed every 6 months ± 7 days to assess the following:

Physical examination and vital signs	• Blood pressure, pulse rate, body temperature • Body weight • Physical examination

Cardiac safety	• 12-Lead ECG and LVEF assessments will be performed 6 and 12 months after completion of trastuzumab treatment
Immunogenicity assessment	A sample for immunogenicity will be taken at the follow-up visit of one year
In patients who underwent surgery: Disease progression	• Survival/death • Progression of disease

Follow-up will be continued for a period of 2 years after completion of treatment or until death, whichever occurs first, per patient or end of study as defined below, whichever is first.

5.3 Planned treatment of the patient after end of treatment phase

After completion of the study, i.e. after end of treatment (EOT), patients will generally be treated at the discretion of the investigator according to medical routine.

5.4 Removal of patients from treatment

Subjects will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/removed if necessary to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided. Only patients withdrawing consent before the end of the neoadjuvant period will be replaced.

Patients will be removed from further treatment for the following reasons:

- Disease progression
- Non-compliance
- Need of treatment with medications not allowed by the study protocol
- Patient no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient
- Investigator decision
- Pregnancy
- Termination of the study by the sponsor

If there is a medical reason for withdrawal of treatment, the patient will remain under the supervision of the investigator until the AEs have been resolved or declined to baseline values. If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the case report form.

If a patient has failed to attend scheduled assessments in the study, the investigator must determine the reasons and circumstances as completely and accurately as possible.

In case of premature discontinuation of the study treatment, the investigations scheduled for the EOT and the follow-up visits should be performed, if possible. The eCRF section entitled “End of Treatment (Adjuvant or Neo-adjuvant, as applicable)” must be completed in all cases. Patients who prematurely discontinued before surgery will be followed-up for safety, but not for progression and survival. All patients who withdraw after surgery will be followed for safety, progression, and survival.

Should a patient decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible. The investigator should contact the patient to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made, with an explanation of why the patient is withdrawing from the study.

If a patient withdraws consent for further study treatment, the patient should still be followed-up, similarly as for other patients who prematurely discontinued. If a patient withdraws consent for further participation in the study, follow-up assessments will be discontinued.

5.5 Study discontinuation

The whole study may be discontinued at the discretion of the sponsor in the event of any of the following:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients

6 INVESTIGATIONAL PRODUCT

6.1 Investigational medicinal product (IMP)

The investigational product (150 mg of active product per vial) will be presented as individually numbered treatment sets to cover the following dose regimes:

- Loading dose neoadjuvant (8mg/kg) – cycle 1
- Maintenance dose for neoadjuvant period (6mg/kg) – cycle 2 - 8
- Loading dose for adjuvant period (8mg/kg) – cycle 9
- Maintenance dose for adjuvant period (6mg/kg) – cycle 10 - 18

An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

IMPs: The test product in this study is HD201 (trastuzumab biosimilar). Herceptin® (trastuzumab) is used as reference therapy.

Docetaxel, epirubicin and cyclophosphamide are not considered IMP as the treatment is according standard of care. Any docetaxel, epirubicin and cyclophosphamide with marketing authorisation in the member state can be administered according to protocol.

The investigator or other appropriate individual, who is designated by the local principal investigator, should maintain records of the inventory at the site, the use for each patient and delivery, storage, and destruction. Investigators should maintain records that adequately document that patients were provided the doses specified in the protocol and reconcile all investigational products received from the sponsor.

6.2 Preparation and administration of trastuzumab (HD201 and Herceptin®)

6.2.1 Preparation and administration of trastuzumab (HD201 and Herceptin®)

6.2.1.1 Drug name, formulation, and storage

Test product

Drug name:	HD201
Active ingredient:	Trastuzumab (proposed biosimilar)
Background information:	Trastuzumab is a recombinant, humanised IgG1 monoclonal antibody. The antibody is directed against the extracellular domain of HER2. HD201 is being developed as a biosimilar of the EU approved trastuzumab (Herceptin®).
Formulation:	HD201 is a freeze-dried preparation. Each vial contains 150 mg powder for concentrate for solution for infusion. Trastuzumab is formulated in histidine, trehalose, and polysorbate 20. Once reconstituted, each solution contains 21 mg/mL of active drug at a pH of approximately 6.0.

Reference therapy:

Drug name:	Herceptin®
Active ingredient:	Trastuzumab
Background information:	Trastuzumab is a recombinant, humanised IgG1 monoclonal antibody. The antibody is directed against the extracellular domain of HER2.
Formulation:	Herceptin® is a freeze-dried preparation. Each vial contains 150 mg powder for concentrate for solution for infusion. Trastuzumab is formulated in histidine, trehalose, and polysorbate 20. Once reconstituted, each solution contains 21 mg/mL of active drug at a pH of approximately 6.0.

Vials of trastuzumab are shipped at a temperature ranging from 2–8°C (36°F–46°F), and must be placed in a refrigerator (same temperature range) immediately upon receipt to ensure optimal retention of physical and biochemical integrity and should remain refrigerated until immediately prior to use. Temperature logs must be maintained (in accordance with local pharmacy practice) on the refrigerator to ensure proper storage conditions. If a temperature deviation from the allowed 2°C−8°C is found either during shipment or storage, contact the sponsor immediately to determine if the drug is still appropriate for use.

DO NOT FREEZE and DO NOT SHAKE the trastuzumab vials. Store all vials within the outer carton, and protect them from light.

The medication must not be used beyond the expiration date stamped on the outer carton and on the vials.

6.2.1.2 Route of administration

Trastuzumab (HD201 / Herceptin®) will be administered by intravenous infusion.

6.2.1.3 Preparation of trastuzumab (HD201 and Herceptin®)

Each vial of trastuzumab 150 mg is reconstituted with 7.2 mL of Sterile Water for Injection (SWFI). This formulation does not contain a preservative and is suitable for single use only.

Appropriate aseptic techniques should be used. Trastuzumab should be carefully handled during reconstitution. The following instructions must be followed:

1. Using a sterile syringe, slowly inject the sterile water for injections in the vial containing the lyophilized trastuzumab, directing the stream into the lyophilized cake.
2. Swirl vial gently to aid reconstitution. DO NOT SHAKE!

The reconstituted solution contains 20.83 mg/mL(wherein 21mg/mL is used for the calculation of the volume of the solution) of trastuzumab, at a pH of approximately 6.0, and the appropriate calculated volume will be added in to 250 mL of 0.9% Sodium Chloride Injection.

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted trastuzumab results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

Trastuzumab should not be mixed or diluted with other drugs. Do not administer as an i.v. push or bolus dose.

Determine the volume of the solution required based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent dose of 6 mg trastuzumab/kg body weight:

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

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with glucose-containing solutions, since it causes aggregation of the protein. The bag should be gently inverted to mix the solution to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration.

Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for a maximum of 24 hours from reconstitution (do not store above 30°C). No incompatibilities between trastuzumab and polyvinylchloride or polyethylene bags have been observed.

Trastuzumab may be sensitive to shear-induced stress (e.g., agitation or rapid expulsion from a syringe). DO NOT SHAKE. Vigorous handling of solutions of trastuzumab results in aggregation of the protein and may create cloudy solutions. Trastuzumab should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted trastuzumab may result in problems with the amount of trastuzumab that can be withdrawn from the vial.

6.2.1.4 Drug Accountability

Accountability will be assessed by maintaining adequate drug dispensing and return records. Accurate records must be kept for each study drug provided by the sponsor (HD201 and Herceptin®)
The drug accountability, dispensing and temperature excursion logs must be available for verification by a CRA during monitoring visits. All supplies, including partially used, damaged, expired or empty vials of trastuzumab and a copy of all logs, must be retained at the site, unless destruction has been authorised.

6.2.2 Preparation and administration of docetaxel, epirubicin and cyclophosphamide

Docetaxel, epirubicin and cyclophosphamide will be obtained locally by the investigational sites. Refer to the Package Inserts of docetaxel, epirubicin and cyclophosphamide for information on formulation, preparation, and administration.

6.3 Dose delays and modifications

If trastuzumab treatment is delayed, then also chemotherapy is delayed, with both treatments reinitiated on the same day if the dosing delay was 7 days or shorter. If the dosing delay is longer than 7 days, chemotherapy and trastuzumab may be uncoupled and given on different days as clinically indicated, but administrations should be brought back to a common administration schedule as soon as possible.

NCI-CTCAE Version 4.03 will be used to grade toxicity. Before starting a new treatment cycle, toxicity must have resolved as specified in the following sections.

6.3.1 Dose delays and modifications for trastuzumab (HD201 / Herceptin®)

Trastuzumab dose reduction/modifications are not permitted.

Trastuzumab doses may be delayed due to toxicities and re-initiated as described in Section 6.3 and 6.3.1.3. If trastuzumab is withheld for more than two cycles or needs to be permanently discontinued, the patient will be withdrawn from all study treatment, and the patient will continue to be followed post-treatment as described in Section 5.2.7.

Trastuzumab administration may be delayed to assess or treat AEs such as cardiac adverse events, myelosuppression, or other events.

6.3.1.1 Cardiac safety

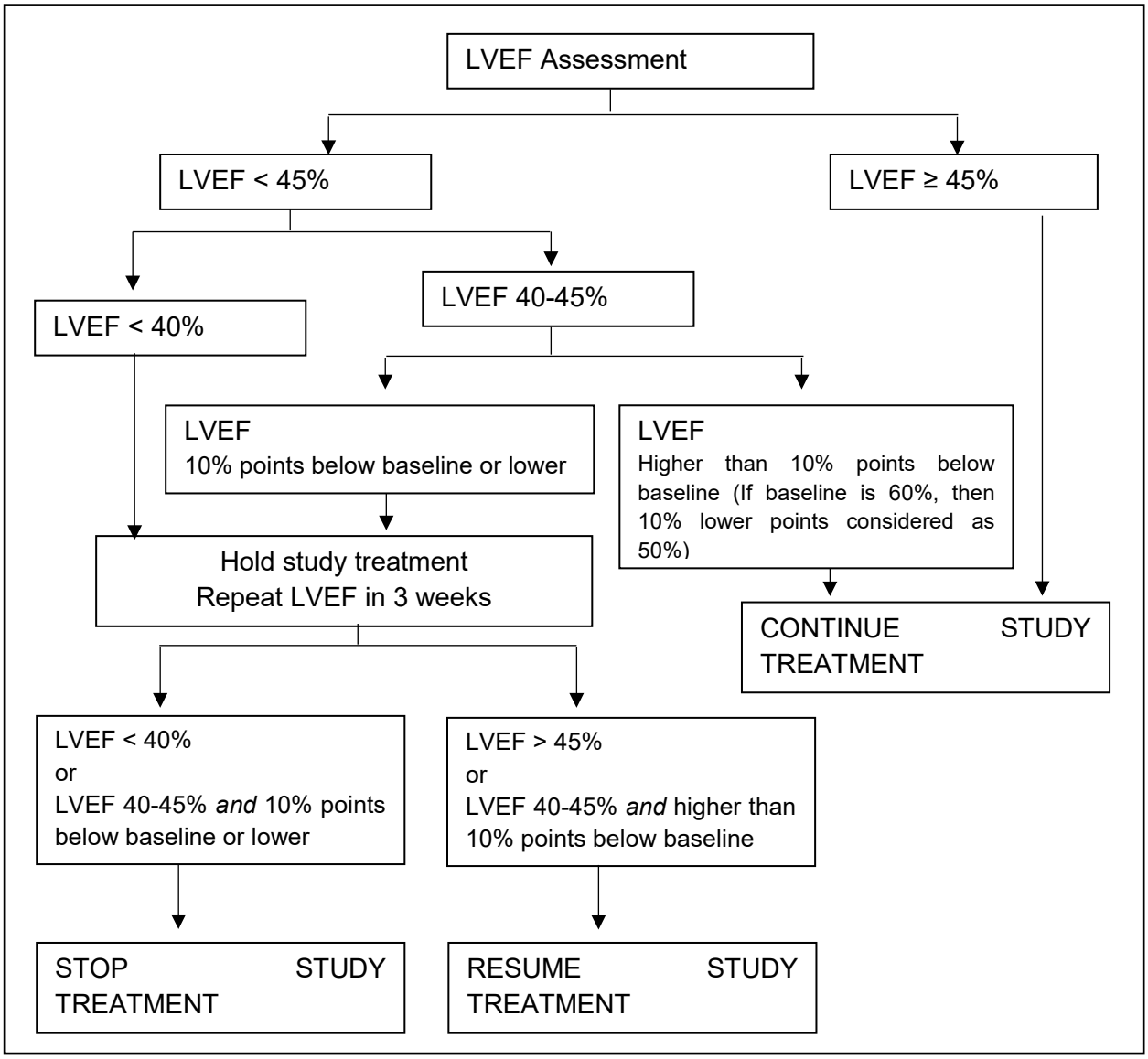
All patients must have a baseline LVEF ≥ 50% or within the normal level of the institution. LVEF will be monitored regularly according to the schedule of assessments. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement should be performed.

Trastuzumab will be discontinued in any patient who develops clinical signs and symptoms suggesting congestive heart failure and a drop in LVEF by ECHO or MUGA. Congestive heart failure should be treated and monitored according to standard medical practice.

To ensure the safety of patients in the trial, trastuzumab must be discontinued in all patients for whom a drop of LVEF to a value lower than 40% is documented and confirmed with a repeat assessment within 3 weeks of the first assessment, using the same assessment method.

For patients whose LVEF drops to values lower than 45%, the decision to stop or continue study treatment is based on the algorithm shown in figure 2.

Figure 2 Algorithm for continuation and discontinuation of trastuzumab based on LVEF assessment



Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 18 weeks, until the LVEF values return to ≥ 50%, or 1 year, whichever comes first.

6.3.1.2 Infusion-associated symptoms and allergic reactions

Administration of monoclonal antibodies, including trastuzumab, may cause infusion-associated symptoms such as chills, fever, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting, or headache. Also, dyspnoea, hypertension, supraventricular tachyarrhythmia, anaphylaxis, urticarial and angioedema have been reported. It is estimated that approximately 40% of patients treated with trastuzumab will experience some form of infusion-related reaction.

Study treatment will be administered in a setting with emergency equipment and staff that is trained to monitor for and respond to medical emergencies. Patients who experience an NCI-CTCAE grade 4 allergic reaction, acute respiratory distress syndrome, or bronchospasm will be discontinued from study treatment.

Patients who experience infusion-associated symptoms may be managed by:

- Slowing or stopping the trastuzumab or chemotherapy infusion
- Supportive care with oxygen, beta agonists, antihistamines, antipyretics, or corticosteroids as appropriate at the investigator's discretion

Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent trastuzumab infusions at the investigator’s discretion.

If infusion-associated symptoms occur, patients will be monitored until complete resolution of signs and symptoms.

6.3.1.3 Incomplete loading dose

In case the whole loading dose of trastuzumab (neoadjuvant, adjuvant, after interruption) could not be administered due to an infusion reaction or other reason, the following guidelines apply:
The patient should receive at least 50% of the loading dose in the first week. Therefore, if the patient receives less than 50% of the Cycle 1 dose, the patient should receive the remainder before Day 22, preferably within the first week. Thereafter, the patient should receive the usual maintenance dose 3 weeks after the first interrupted dose, as routinely scheduled. For example, if a patient received only approximately 50% of the scheduled loading dose (i.e., only 4 mg/kg instead of 8 mg/kg of trastuzumab), the patient should receive the remaining dose (4 mg/kg of trastuzumab), preferably in the first week, and then regular maintenance doses (6 mg/kg of trastuzumab) on Day 22, as routinely scheduled.

If the patient receives between 50–75% of the dose, the patient should receive the remainder before Day 22, preferably within the first two weeks of Cycle 1. For example, if a patient received only approximately 60% of the scheduled loading dose, the patient should receive the remaining 40%, within 2 weeks after the interrupted loading dose. Thereafter, the patient should receive the regular maintenance doses on Day 22, as routinely scheduled.

If the patient received ≥ 75% of the loading dose, additional loading is probably not necessary. However, the remainder of the loading dose may be given at the investigator's discretion. In such a case, the remainder may be given at any time before the next scheduled dose or the patient may be given an additional loading dose on Day 22. If, after receiving an incomplete loading dose on Day 1, the patient cannot attend the site until Day 22, the patient should receive a second loading dose on Day 22. However, every effort should be made to give the remainder of the dose prior to Day 22. Unscheduled visit(s) may be arranged for any remainder dose to be administered.

6.3.2 Dose delays and modifications for docetaxel

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

6.3.2.1 Docetaxel dose adjustments

Docetaxel dose reduction will be allowed for myelosuppression, hepatic dysfunction, and other toxicities (see Table 2).

Table 2: Docetaxel dose adjustments

Docetaxel dose	When
75 mg/m²	Starting dose - Administer only if neutrophil count is > 1500 cell/mm^3
55 mg/m^2	25% reduced dose in case of any of the following toxicities: - Febrile neutropenia or neutrophils < 500 cells/mm^2 for more than 1 week (after fully recovering to a neutrophil count ≥ 1,500 cells/mm^3) - Platelet count < 100,000 cells/mm^3 (after recovering to a platelet count ≥ 100,000 cells/mm^3) - Severe or cumulative cutaneous reactions
Permanently discontinue docetaxel	After any of the following toxicities: - Severe hypersensitivity reactions (Section 6.3.2.3) - Peripheral neuropathy > Grade 3 - Severe or cumulative cutaneous reactions that continue at a dose of 55 mg/m^2 without recovery - Febrile neutropenia or neutrophils < 500 cells/mm^3 without recovery - Platelet < 100,000 cells/mm^3 without recovery - Total bilirubin > ULN without recovery - Serum transaminase (AST/ALT) levels > 1.5 ×ULN concurrent with serum alkaline phosphatase levels > 2.5 ×ULN without recovery

ANC=absolute neutrophil count; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ULN=upper limit of normal.

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

6.3.2.2 Haematotoxicity

6.3.2.2.1 Neutrophil count

Docetaxel should only be administered if the neutrophil count is ≥ 1,500 cells/mm^3.

If patients experience either febrile neutropenia or neutrophils < 500 cells/mm^3 for more than one week following docetaxel administration, docetaxel should be held until the patient is fully recovered and the neutrophil count is ≥ 1,500 cells/mm^3. Treatment with docetaxel may be resumed with a 25% reduction in the dose. If patients continue to experience these reactions at a dose of 55 mg/m^2, docetaxel should be discontinued permanently.

Alternatively, secondary prophylactic G-CSF may be used in patients who experienced febrile neutropenia or severe infection during the previous cycle. G-CSF can also be used as primary prophylactic strategy to maintain dose intensity as clinically indicated or per the ASCO guidelines for growth factor support[31].

6.3.2.2.2 Platelet count

- Patients with a platelet count of ≥ 100,000 cells/mm^3 on the day of treatment may receive docetaxel.
- Patients with a platelet count < 100,000 cells/mm^3 should not be given docetaxel. Docetaxel may be delayed for a maximum of 3 weeks.
- If the platelet count recovers to ≥ 100,000 cells/mm^3 after a decline to < 100,000 cells/mm^3, the patient should receive further cycles of docetaxel with a 25% reduction in the dose.
- If the platelet count does not recover to a level ≥ 100,000 cells/mm^3, the patient should discontinue docetaxel.

6.3.2.3 Hypersensitivity

Patients should be observed closely for hypersensitivity reactions, especially during the first and second docetaxel infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel; thus, facilities for the treatment of hypotension and bronchospasm should be available.

Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who received the recommended 3-day dexamethasone premedication.

Hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and administration of appropriate therapy. These patients should not be re-challenged with docetaxel. Docetaxel must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80.

Minor symptoms such as flushing or localized cutaneous reactions generally do not require interruption of therapy.

6.3.2.4 Peripheral neuropathy

Patients who develop ≥ Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

6.3.2.5 Fluid retention

Severe (Grade 3 or 4) toxicity such as pleural effusion, pericardial effusion, or ascites that is possibly related to docetaxel should be closely monitored and the decision to continue or discontinue study treatment is at the discretion of the Investigator.

6.3.2.6 Hepatic impairment

Patients should have adequate baseline liver function as stated in the inclusion criteria in Section 4.2. Liver function should be measured before each cycle to avoid docetaxel-associated toxicity.

According to the manufacturer, docetaxel should not be administered to patients who have total bilirubin > ULN or to patients with serum transaminase (AST/ALT) levels > 1.5 × ULN concurrent with serum alkaline phosphatase levels > 2.5 × ULN, as there is a higher risk of developing adverse reactions such as toxic death, including sepsis; gastrointestinal haemorrhage, which can be fatal; febrile neutropenia; infections; thrombocytopenia; stomatitis; and asthenia.

6.3.2.7 Cutaneous reactions

Localized skin erythema of the extremities with edema followed by desquamation has been observed. If the patient experiences these reactions at a dose of 75 mg/m^2, the dose should be reduced to 55 mg/m^2 or the treatment should be discontinued.

6.3.3 Dose delays and modifications for epirubicin

Epirubicin may be delayed due to toxicities. If epirubicin is delayed for more than 3 weeks with no recovery, the patient should be withdrawn from epirubicin treatment. If epirubicin needs to be permanently discontinued, the patient may continue trastuzumab and cyclophosphamide.

Dosage adjustments should be made based on haematologic and non-haematologic toxicities. Patients experiencing platelet counts < 100,000 cells/mm³, absolute neutrophil counts (ANC) < 1,500 cells/mm³, neutropenic fever, or grade 3/4 non-haematologic toxicities should have the dose in subsequent cycles reduced to 75% of the initial dose. Chemotherapy in subsequent cycles should be delayed until platelet counts are ≥ 100,000 cells/mm³, ANC ≥ 1,500 cells/mm³, and non-haematologic toxicities have recovered to ≤ grade 1.

Further recommendations given in the prescribing information for epirubicin should be strictly followed.

6.3.3.1 Hepatic impairment

The major route of elimination of epirubicin is the hepatobiliary system. In patients with impaired liver function the dose should be reduced based on serum bilirubin levels as follows:

Serum bilirubin	AST/SGOT	Dose reduction

1.4 – 3 mg/100mL		50%
> 3 mg/100mL	>4 times ULN	75%

6.3.3.2 Impaired renal function

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route. However, dosage adjustment may be necessary in patients with serum creatinine > 5 mg/dL.

6.3.4 Dose delays and modifications for cyclophosphamide

Cyclophosphamide may be delayed due to toxicities. If cyclophosphamide is delayed for more than 3 weeks with no recovery the patient should be withdrawn from cyclophosphamide treatment. If cyclophosphamide needs to be permanently discontinued, the patient may continue on trastuzumab and epirubicin.

As with epirubicin, dosage adjustments should be made based on haematologic and non-haematologic toxicities. Patients experiencing platelet counts < 100,000 cells/mm³, absolute neutrophil counts (ANC) < 1,500 cells/mm³, neutropenic fever, or grade 3/4 non-haematologic toxicities should have the dose in subsequent cycles reduced to 75% of the initial dose. Chemotherapy in subsequent cycles should be delayed until platelet counts are ≥ 100,000 cells/mm³, ANC ≥ 1,500 cells/mm³, and non-haematologic toxicities have recovered to ≤ grade 1.

Further recommendations given in the prescribing information for cyclophosphamide should be strictly followed.

6.3.4.1 Hepatic impairment

Give 75% of normal dose if transaminase levels are > 3 x ULN or bilirubin is 3.1-5 mg/dL.

6.3.4.2 Impaired renal function

Caution is recommended when used in patients with renal dysfunction. The dose should be reduced when the creatinine clearance is < 10 mL/min.

6.3.5 Dose adjustment for changes in body weight

Baseline body weight is used to calculate required doses of trastuzumab and chemotherapy.

The trastuzumab dose should be recalculated only if the patient’s weight changes by ±10% from baseline.

Docetaxel, epirubicin and cyclophosphamide dose adjustments due to changes in body weight should be based upon the investigative site’s institutional standards.

6.4 Concomitant medication and treatment

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

All protocol-allowed medications taken by the patient for concomitant disease should continue as necessary during the study and be recorded on the electronic case report form (eCRF). The following list of allowed medications is provided as guidance. Treatments prescribed to patients should be adapted according to the local standard of care practice.

6.4.1 Permitted treatments/procedures:

- Paracetamol (acetaminophen) or other analgesics, and diphenhydramine, chlorpheniramine, or other antihistamines can be used according to local clinical practice for the prevention and treatment of infusion reactions.
- Medication to treat diarrhoea (e.g., loperamide).
- Granulocyte colony stimulating factor (G-CSF) may be used according to the product license and according to the currently approved prescribing information for chemotherapeutic agents and ASCO clinical guidelines[31].
- Steroids for chemotherapy premedication and anti-emetics according to routine practice at each clinical site.
- Inhaled steroids for asthma.
- Bisphosphonates may be given according to their product license and routine clinical practice, at the investigator's discretion.
- Surgical procedures. Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded including the dates, description of the procedure(s), and any clinical findings.
- As a precautionary measure, it is recommended, but not strictly required, that if patients require placement of a central venous access device (CVAD), that procedure should be done 7 days prior to first study treatment start.
  The date of CVAD placement should be noted in the medical record and recorded in the eCRF. Episodes of CVAD replacement should be recorded, as should CVAD related thrombosis, infection, or dysfunction.
- Anti-coagulation therapy for maintenance of patency of permanent indwelling i.v. catheters is permitted.

6.4.2 Prohibited medications

Patients should not receive any of the following medications during the treatment period:

- Treatment with other systemic anti-cancer agents (e.g., chemotherapy, hormonal therapy, immunotherapy) or other treatments not part of protocol-specified anti-cancer therapy. *Note: During the adjuvant period, patients may receive hormone therapy or radiotherapy or both.*
- Concurrent investigational agents of any type.
- Initiation of herbal remedies for cancer treatment. Herbal remedies initiated prior to study entry and continuing during the study are permitted and must be reported on the appropriate eCRF.

The following treatments should be avoided because of the risk of immunosuppression:

- Chronic or high-dose oral corticosteroid therapy.
- TNF-α inhibitors.
- Anti–T cell antibodies.

6.4.3 Advice regarding specific medical conditions and procedures

All those treatments should be stopped before randomization: Concurrent hormonal therapy including birth control pills, ovarian hormone replacement for menopause, selective oestrogen receptor modulator (SERM) either for osteoporosis or breast cancer prevention.

Axillary lymph node dissection (ALND) is recommended. Lymph node axillary dissection must include the first and second level. Nevertheless, sentinel node biopsy is allowed as a possible therapeutic option in cN0 before neo-adjuvant therapy and 3 to 5 “sentinel nodes” are recommended to minimize the false negative rate. Sentinel node biopsy must be followed by ALND if positive involved nodes are found. When the sentinel node biopsy is negative a full axillary dissection is not requested after the neo-adjuvant chemotherapy.

Surgery should be performed according to procedures decided by the local surgeon who should consider tumour size, breast volume, and patient's attitude. Conservative surgery is not recommended for inflammatory breast cancer or in the presence of extensive microcalcifications. Whenever possible, in operable and locally advanced non-inflammatory cancer, conservation methods should be preferred. Conservation should consist of a wide resection, with safe free margins. To perform this conservative surgery the inclusion inside the tumour of a clip to allow the identification of the tumour bed by the surgeon especially when all tumour disappear due to the efficacy of treatment. The inclusion of such clip is optional but might facilitate an optimal resection. The clip can be included at baseline or while the patient receives the neo-adjuvant therapy according to the clinically or ultrasound monitoring of tumour progressive shrinkage.

6.5 Warnings, precautions and risk assessment

6.5.1 Warnings, precautions and risks for trastuzumab

Trastuzumab therapy should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

Serious adverse reactions including cardiotoxicities, infusion reactions, hypersensitivity, allergic-like reactions, and pulmonary events have been observed in patients receiving trastuzumab therapy. These severe reactions were usually associated with the first infusion of trastuzumab and generally occurred during or immediately following the infusion. For some patients, symptoms progressively worsened and led to further pulmonary complications.

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than 6 hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur. Patients who have dyspnoea at rest due to co-morbidities may be at increased risk of a fatal infusion reaction and should therefore not be treated with trastuzumab.

The impact algorithm assessment is as follows:

		Serious (Eudravigilance always serious list + AEs reported as being associated with fatal outcomes according to Herceptin SmPC)			
		Yes		No	
Frequency as per SmPC for Herceptin	Very common or common	High risk + Undetectable and or untreatable CATASTROPHIC impact	High risk + Detectable and treatable MAJOR impact	Medium risk + Undetectable and or untreatable MAJOR impact	Medium risk + Detectable and treatable MODERATE impact
	Rare or unknown	Medium risk + Undetectable and or untreatable MAJOR impact	Medium risk + Detectable and treatable MODERATE impact	Low risk + Undetectable and or untreatable MINOR impact	Low risk + Detectable and treatable MINOR impact

The categories of frequency are described as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

6.5.1.1 Infusion reactions, allergic-like reactions, and hypersensitivity

Serious adverse reactions to trastuzumab infusion that have been reported include:

- dyspnoea (very common), hypotension (common), wheezing (very common), hypertension (very common), supraventricular tachyarrhythmia (common). These are High Risk reactions and as they are detectable and treatable, their impact is MAJOR.
- reduced oxygen saturation (not known), anaphylactic reaction (not known), anaphylactic shock (not known), bronchospasm (not known), and respiratory distress (not known). These are Medium Risk reactions and as they are detectable and treatable their impact is MODERATE.

Most of these events occur during or within 2.5 hours of the start of the first infusion.

Should an infusion reaction occur, the trastuzumab infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of any observed symptoms. The symptoms can be treated with analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Most patients experienced resolution of symptoms and subsequently received further infusions.

Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions were associated with a clinical course culminating in a fatal outcome. Patients with dyspnoea at rest due to co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab.

6.5.1.2 Pulmonary events

Dyspnoea (very common), asthma (common), and hypoxia (common) can occur as part of an infusion reaction. These are most common with the first infusion, and their severity decreases with subsequent infusions. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids.
The reactions mentioned above are High Risk reactions and as they are detectable and treatable, their impact is MAJOR.

Furthermore, the following cases have been reported with a fatal outcome:

- wheezing (very common), pneumonia (common), pleural effusion (common). These are High Risk reactions and as they are detectable and treatable, their impact is MAJOR.

bronchospasm (not known), pulmonary infiltrates (not known), pulmonary fibrosis (not known), respiratory distress (not known), acute pulmonary oedema (not known), and respiratory insufficiency (not known), decreased oxygen saturation and acute respiratory distress syndrome (ARDS) (not known). These are Medium Risk reactions and as they are detectable and treatable their impact is MODERATE.

6.5.1.3 Cardiotoxicity

Heart failure (NYHA Class II–IV) has commonly been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death.
Risk factors for trastuzumab-associated cardiotoxicity include increased age, concomitant administration with anthracyclines, and declining LVEF while on trastuzumab treatment. If symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with the standard medications for this purpose.

Trastuzumab may persist in the circulation for up to 7 months after stopping treatment based on population pharmacokinetic analysis of all available data. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully. *Note: In the neoadjuvant setting, trastuzumab should be used in combination with anthracyclines only in chemotherapy-naïve patients and only with low-dose anthracycline regimens, i.e. maximum cumulative doses of doxorubicin 180 mg/m² or epirubicin 360 mg/m². The maximum cumulative dose of epirubicin in this protocol is 300 mg/m².*

Trastuzumab has known side effects related to the heart. The use of other chemotherapy drugs such as Epirubicin and Cyclophosphamide which will be given as treatment during this study also can have heart related side effects. However previous studies have shown that if Trastuzumab and Epirubicin/cyclophosphamide are given together heart related side effects are not increased. Nevertheless, an increase in heart related side effects cannot be excluded.

Cardiotoxicity reactions are considered High Risk and as they are detectable and treatable, their impact is MAJOR.

Summary:
The impact algorithm assessment shows cardiotoxicities as high risks with a moderate to major impact on the patient; infusion reactions, allergic-like reactions, hypersensitivity, and pulmonary reactions as medium to high risks with moderate to major impact on the patient. The biosimilar tested HD201 is expected to show similar risks.

6.5.2 Warnings, precautions and risks for docetaxel, epirubicin and cyclophosphamide

No evidence available at the time of finalisation of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the currently approved prescribing information for docetaxel, epirubicin and cyclophosphamide.

Risks are as per standard practice.

7 ASSESSMENT OF SAFETY

The Investigator's Brochure of HD201 will be used as reference document for the IMP and will be provided to the investigators in the Investigator Site File.

7.1 Adverse events and laboratory abnormalities reporting according to ICH Harmonised Tripartite Guideline, Clinical Safety Data Management

7.1.1 Adverse event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

7.1.2 Adverse drug reaction

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established:
all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.
The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
Regarding marketed medicinal products, a well-accepted definition of an adverse drug reaction (ADR) in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows:
A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.
The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

7.1.3 Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

7.1.4 Serious Adverse Event or Adverse Drug Reaction

During clinical investigations, adverse events may occur which, if suspected to be medicinal product related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population,

needed monitoring, consent forms). This is particularly true for reactions which, in their most severe forms, threaten life or function. Such reactions should be reported promptly to regulators.

PLEASE NOTE: Death is not an event. It is an event outcome. Please document the event which results in death on the SAE report from.

7.1.5 NOT to be reported as SAEs

For this study, the following conditions or planned events are not classified as serious adverse events:

- Progression, deterioration, or other events secondary to the malignancy under study (including metastatic lesions) or death due to progression.
- Hospitalisation for the performance of protocol-required procedures or administration of study treatment. However, hospitalisation or a prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or procedures planned prior to study start. A pre-planned procedure must be documented in the source documents. However, hospitalisation or a prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- An elective hospitalisation for a pre-existing condition unrelated to the study indication.
- Hospital admission that is not associated with an adverse event (e.g. social hospitalisation for purpose of respite care).
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalisation or a prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

7.1.6 SUSAR / Suspected unexpected serious adverse reaction

A SUSAR is defined as a suspected unexpected serious adverse reaction. An unexpected adverse reaction is any adverse drug reaction, the specificity or severity of which is not consistent with the current investigator's brochure for HD201. Also, reports that provide significant information on the specificity or severity of a known, already documented adverse event constitute unexpected adverse events. An adverse reaction more specific or more severe than described in the investigator's brochure would be considered "unexpected". All suspected adverse reactions related to HD201 which occur in the trial and that are both unexpected and serious (SUSARs / Suspected unexpected serious adverse reactions) are subject to expedited reporting.

7.2 Reporting of SAEs

Any serious clinical adverse event or clinically significant abnormal laboratory test value occurring during the course of the study from the date of signing the informed consent, irrespective of the treatment received by the patient, must be reported to the sponsor within 24

hours of knowledge (expedited reporting). For each patient, all serious adverse events must be reported up to 7 months after the last dose of investigational product. Serious adverse events occurring more than 7 months after a patient is discontinued from the study treatment may be reported at the discretion of the investigator.

The completed SAE form must be transmitted to

Address: [redacted]

Phone: [redacted]

Email: [redacted]

The sponsor will medically review all SAEs.

The following detailed information must be recorded for each serious adverse event in the SAE report form:

- A description of the AE in medical terms according to NCI-CTC Version 4.03*,* not as reported by the subject.
- The severity grade as assessed by the investigator according to the definitions in NCI-CTC Version 4.03.
- The date of becoming serious and the date of becoming known (if different).
- The reason for seriousness.
- The outcome of the SAE at the time of the report.
- Information of administration of the study drug and any action taken.
- Information on any treatment procedures necessary for the SAE, concomitant medications, relevant lab tests and relevant medical history.

If in any one patient the same SAE occurs on several occasions, then the SAE in question must be documented and assessed anew each time.

The investigator is required to submit SAE Follow-up reports until the SAE has resolved or stabilized and all queries have been answered.

7.3 Reporting of SUSARs

The sponsor will ensure the notifications of the appropriate ethics committee, competent authorities, and participating investigators of all SUSARs occurring at the sites in accordance with local legal requirements, statutes and the European Clinical Trial Directive as follows:

- Reporting of the SUSAR to the Competent Authorities and Ethics Committees within 15 days (or within 7 days for fatal and life-threatening events).

- Sending the SUSAR report to all participating investigators for information (with confirmation of receipt).

In addition, all events that require a new assessment of the risk-benefit ratio will be reported to the Ethics Committee and the Competent Authority of each concerned Member State within 15 days. This include:

- Single reports of expected serious adverse reactions with unexpected outcome.
- An increase in the rate of occurrence of expected serious adverse reactions which is judged to be clinically relevant.
- Post-study SUSARs that occur after the patient has completed a clinical trial.
- New events related to the conduct of the trial or the development of the investigational medicinal products and likely to affect the safety of the subjects.

7.4 Recording of adverse events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by patients are properly and no later than 7 days after patients visit recorded in the patient's medical records and the case report form.

Adverse events are collected from signing the ICF until 7 months after the last administration of treatment. AEs for which the relationship to test drug is not "unrelated" should be followed up until they have returned to baseline status or stabilised.

The following adverse event attributes must be assigned by the investigator:

- Adverse event term according to the NCI-CTC criteria Version 4.03
- Severity grade according to NCI-CTC criteria Version 4.03
- Start date and stop date (or date of last assessment)
- Outcome
- Causality to study drug and chemotherapy (to be assessed as
    - Unrelated:

the event is definitely not associated with study drug administration/chemotherapy, but is judged clearly and incontrovertibly due to causes other than the study medication/chemotherapy.

    - Unlikely:

an event that follows such a temporal sequence from administration of the study medication/chemotherapy that a relationship is not likely, and is likely to be due to a cause such as (known characteristics of) the patient's clinical state or other treatment.

    - Possible:

an event that follows a reasonable temporal sequence from administration of the study medication/chemotherapy, but that may be due to another cause.

    - Probable:

an event that follows a reasonable temporal sequence from administration of the study medication/chemotherapy, and that is not easily explained by another cause such as known characteristics of the patient's clinical state or other treatment.

- Definite:

An event that follows an established temporal sequence from administration of the study medication/chemotherapy (e.g. re-challenge), or that cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s).

- Any action taken

Adverse events will be followed until they resolve to baseline or considered stable. It will be left to the investigator's clinical judgement to determine whether an adverse event is related and of sufficient severity to require the patient's removal from treatment or from the study. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arise, the patient should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), v4.03 (see investigator's file). If an adverse event occurs which is not described in the CTCAE v4.03, the four-point scale below will be used.

Mild: Discomfort noticed but no disruption of normal daily activity
Moderate: Discomfort sufficient to reduce or affect daily activity
Severe: Inability to work or perform normal daily activity
Life-threatening: Represents an immediate threat to life

7.5 Laboratory test abnormalities

Laboratory test results will be recorded on the laboratory results pages of the case report form. In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

Laboratory test value abnormalities as such should not be reported on the AE page of the eCRF as adverse events unless they are treatment-emergent, and they satisfy one or more of the following conditions for clinical significance:

1. Accompanied by clinical symptoms
2. Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
3. Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

Please note: Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an adverse event in the eCRF.

7.6 Pregnancy

Female patients must be instructed to immediately inform the investigator if they become pregnant during the study. The study treatment must immediately be stopped, and the patient must be withdrawn from the study. Pregnancies occurring up to 7 months after the completion of the last treatment cycle must also be reported to the investigator. The investigator must report all pregnancies within 24 hours of knowledge to [redacted] will forward all pregnancy reports to the sponsor within 1 working day. The investigator should counsel the patient, discuss the risks of continuing the pregnancy and the possible effects on the foetus. The patient should be monitored until the end of the pregnancy.

7.7 Adverse drug reactions with concomitant medication

The investigators must be aware that for all concomitant medications the regulations of post-marketing reporting for suspected adverse drug reactions apply, i.e. reporting to the marketing authorisation holder or the local regulatory bodies.

7.8 Safety surveillance

SAE and SUSAR overview lists will be sent to the DMC on a 6-monthly basis for safety monitoring.

8 BIOSTATISTICAL ASPECTS

8.1 Trial design and hypotheses

This is a randomised, double-blind, parallel group, equivalence, multicentre phase III trial.

Patients will be randomised in a 1:1 ratio to HD201 or reference Herceptin®, and stratified by

- Geographical region
- Clinical stage (stage II vs. III)
- E2/P4 receptor status (both negative versus at least one positive)

The primary objective of the study is to compare tpCR in patients treated with HD201 plus chemotherapy to that in patients treated with Herceptin® plus chemotherapy. The tpCR will be assessed at the time of surgery after neoadjuvant treatment completion after 24 weeks.

The primary hypothesis is that the tpCR rate is equivalent in the two treatment groups. Equivalence will be concluded if the 95% confidence interval on the difference of the two proportions is completely contained within the interval [-15.0;+15.0].

tpCR will be assessed both by local and by central reading. The primary endpoint will be tpCR as assessed by local reading. A supportive analysis will be performed, using the same approach, considering tpCR assessed by central reading.

Secondary efficacy variables are bpCR and ORR assessed at the time of surgery after neoadjuvant treatment completion after 24 weeks, and OS and EFS two years after end of study treatment.

The null hypothesis to be tested for the secondary efficacy endpoints is that there is no difference between HD201 and Herceptin®. The alternative hypothesis is that there is a difference between HD201 and Herceptin®.

The hypotheses can be formally stated as:
H_0: $\pi_{HD201} = \pi_{Herceptin®}$, H_1: $\pi_{HD201} \neq \pi_{Herceptin®}$
where π is the rate for each treatment group.

The secondary efficacy variables will be analyzed based on two-sided tests at the 5% level of significance. No adjustments will be made to non-primary endpoints for multiplicity.

8.2 Sample size calculation

It is planned that 500 patients will be randomised to ensure completion of 450 patients (10% drop-out rate assumed). The sample size calculation was based on results from many randomized trials with data for tpCR[11,16,18,22,32]. The following assumptions are made:

- the true difference in proportions is 0.00
- the proportion in the reference group is 0.40 (Gianni et al[11])

- the equivalence margin is +/- 0.15 This margin has been motivated by the objective of preserving 60% of the magnitude of the benefit of trastuzumab in terms tpCR, similarly to Stebbing et al[32]

To have 80% power of showing equivalence data should be available for 224 patients per treatment group. Considering approximately 10% drop-outs or non-evaluable patients a total of 500 patients are to be randomized to ensure that sufficient patients complete the study without compromising the power of the study.

8.3 Analysis sets

The following analysis sets will be considered:

Total Set: All patients who consented to participate in the study.

Intent-to-treat (ITT) Population: All patients of the Total Set who were randomised and received at least one dose of study medication (HD201 or Herceptin®).

Per Protocol (PP) Population: All patients of the ITT Population who received the study treatment according to the protocol, without any major protocol deviation impacting the primary efficacy assessment, and who had surgery after completion of neoadjuvant treatment or did not undergo surgery due to lack of efficacy.

Safety Population: All randomized patients who received at least one dose of study medication (HD201 or Herceptin®).

For the ITT Population patients will be considered in the treatment group as randomized (as foreseen by the attributed randomization number). For the other analysis sets patients will be considered in the treatment group as treated.

The exclusion of patients from the analysis sets will be discussed during a blind review meeting that will be held before database lock.

The efficacy analyses will be performed for the ITT Population and the PP Population. The primary set for the analysis of the primary efficacy variable is the PP Population. For the secondary efficacy variables, the primary analysis set is the ITT Population.

8.4 Methods of statistical analysis

The statistical methods outlined in the protocol will be detailed in the statistical analysis plan (SAP) which will be created and finalised before the opening of the treatment code.

8.4.1 General Statistical Considerations

The statistical analysis will be performed using the SAS statistical package, version 9.2 or later.

Unless otherwise stated, summary statistics for quantitative variables will include the mean, standard deviation (SD), 95% confidence interval on the mean, minimum, 1st quartile, median, 3rd quartile, maximum, number of observations, and number of missing values. For categorical variables, absolute counts (n) and percentages (%) of patients with data will be presented. For key categorical variables exact 95% confidence intervals (CI) will be presented for each treatment group and for the difference or ratio between the 2 groups.

The inferential statistical analysis will consist of:

- For the primary efficacy variable
  - Equivalence testing by comparing the 95% CI on the difference between the 2 treatment groups with the interval [-0.15; +0.15]
  - 95% CI on the ratio between the 2 treatment groups
  - Logistic regression
- For time to event variables:
  - Kaplan-Meier survival analysis
  - Log-rank test
  - Estimate and 95% CI at selected time-point
  - Cox regression. The independent variables to be used will be specified in the SAP.
- For binary secondary efficacy variables:
  - Fisher Exact test
  - Logistic regression

Superiority tests will be performed two-tailed, at the 5% level of significance.

8.4.2 Demographics and baseline characteristics

A description will be given of key patient characteristics recorded at the screening and baseline visits, for all patients and broken down by treatment group.

8.4.3 Efficacy evaluation

8.4.3.1 Primary efficacy variable

The primary efficacy variable of the study is tpCR assessed locally at the time of surgery after neoadjuvant treatment completion. In case tpCR is missing due to lack of efficacy it will be imputed as not reaching the endpoint. In all other cases tpCR will remain missing.

The primary analysis of the primary efficacy variable is an equivalence analysis based on an exact 95% CI on the difference in tpCR rate at the time of surgery. Equivalence will be concluded if the 95% CI on the difference of the two proportions is completely contained within the interval [-15.0;+15.0] .

A secondary analysis of the primary efficacy variable will be performed by means of a logistic mixed model adjusted for treatment, region, stage, and E2/P4 receptor status.

A sensitivity analysis will be conducted in the ITT population for the absolute difference as well as for the success ratio.

8.4.3.2 Secondary efficacy variables

tpCR
tpCR at the time of surgery after neoadjuvant treatment completion after 24 weeks, as assessed by a central laboratory. In case tpCR is missing due to lack of efficacy it will be imputed as not reaching the endpoint. In all other cases tpCR will remain missing. The analysis will be performed in the same way as the primary analysis of the primary efficacy variable.

bpCR
Breast pathological complete response (bpCR) is assessed at time of surgery. The bpCR rate will in first instance be compared in the two treatment groups by means of a Fisher Exact test. A secondary analysis will be performed by means of a logistic mixed model controlling for treatment, stage, and E2/P4 receptor status.

ORR
Overall response is defined as the proportion of patients whose overall response is either CR or PR (CR+PR) at the time of surgery, as derived from Mammography, Ultrasound and clinical assessmentsORR will in first instance be compared in the two treatment groups by means of a Fisher Exact test. A secondary analysis will be performed by means of a logistic mixed model controlling for treatment, stage, and E2/P4 receptor status.

Event Free Survival (EFS)
Event free survival is defined as the time from Day 1 of therapy (day of first infusion of medication on study), until the first observation of disease progression (documented by appropriate imaging techniques) or the date of death due to any cause, if death occurred within 72 days after the last valid tumour assessment. Handling of censoring will be discussed in detail in the SAP.

EFS will be analysed using Kaplan-Meier survival analysis with a comparison of the survival distribution curves for the two treatment groups by means of the log-rank test. The EFS rate and 95% CI at 2 after the end of study treatment will be estimated based on the Kaplan-Meier analysis. A multivariate analysis will be performed by means of Cox proportional hazards.

Overall survival time
The survival time of a patient is defined as the time from Day 1 of therapy to death. For patients who are still alive at the time of study analysis or who are lost to follow up, survival will be censored at the last recorded date that the patient is known to be alive.

OS will be analysed using Kaplan-Meier survival analysis with a comparison of the survival distribution curves for the two treatment groups by means of the log-rank test. The OS rate

and 95% CI at 2 after the end of study treatment will be estimated based on the Kaplan-Meier analysis. A multivariate analysis will be performed by means of Cox proportional hazards.

8.4.4 Safety evaluation

Safety analyses will be performed based on the Safety Set. No formal statistical comparisons are planned.

8.4.4.1 Adverse events

AEs will be graded according to NCI-CTCAE toxicity criteria v. 4.03. and coded according to the Medical Dictionary for Regulatory Affairs (MedDRA). The analysis of AEs will only consider treatment-emergent AEs (TEAEs), defined as AEs with an onset date on or after Day 1 of study therapy and up to the End of Treatment visit within five months from treatment discontinuation. Frequencies will be given of patients with TEAEs, treatment-emergent SAEs (TESAEs), related TEAEs, related TESAEs, TEAEs leading to study discontinuation, TEAEs leading to dose modification or discontinuation of study treatment (HD201 or Herceptin®), broken down by treatment group. The frequency of patients with AEs will be provided:

- Broken down by system organ class.
- Broken down by system organ class and preferred term.
- Broken down by system organ class, preferred term, and maximal NCI-CTCAE v 4.03 grade.
- Broken down by system organ class, preferred term, and strongest relationship. TEAEs reported with a causal relationship of “definitely related”, “possibly related”, “not related” and “unknown relationship/not assessable” to medication will be considered related to treatment. In case of missing relationship assessment TEAEs will be considered as related to the treatment.

Further subgroup analyses may be performed and will be specified in the SAP.

8.4.4.2 Analysis of other safety data

Laboratory results will be classified according to the NCI-CTCAE v. 4.03. The worst on-study grade after the first dose of study treatment will be summarized. Incidence of NCI-CTCAE v. 4.03 Grade 3 or 4 laboratory abnormalities (tests) under treatment and shifts in toxicity grading from treatment start to highest grade will be displayed. Results for variables that were not part of the NCI-CTCAE will be presented with respect to the normal limits of the local laboratory. Only patients with post-baseline laboratory values will be included in these analyses. The last measurement before onset of study treatment will serve as the baseline measurement.

Physical examination and vital signs
Clinically significant abnormal findings from the physical examination and vital sign measurements are to be reported as AEs. Therefore, no separate summaries will be provided of the physical examination data.

Immunogenicity
Immunogenicity data will be summarized and analyzed descriptively for each scheduled protocol assessment time-point (baseline, before cycle 5 (this sample will only be tested if pre-surgery sample is ADA positive), before surgery, post surgery (before cycle 10), before cycle 14 and at EOT visit and one year after completion of trastuzumab treatment), and overall. Cut-off values of each assay were previously determined. Each sample will be assessed as above or below the cut-off.

A listing will be produced showing all immunology results for patients with any confirmed positive result.

ECG
Descriptive statistics will be provided for ECG status at each scheduled protocol assessment time-point.

LVEF
Descriptive statistics will be provided for LVEF at each scheduled protocol assessment time-point.

8.4.4.3 Analysis of PK data

Comparison between two arms are based on $C_{trough.}$ Absolute difference value between the two arms and their 90% confidence interval will be provided. 20% will be considered as margin of equivalence. The evaluation will be performed both at cycle 5 and cycle 8. The analyses will primarily be performed for the PP Population and supportively on the ITT population.
To be noted that PK testing will be performed on the first 320 patient samples to obtain values for approximatively 150 in each arm. The remaining samples will be stored for potential future analysis.

8.5 Intermediate and Final analysis

An intermediate analysis of the efficacy endpoints tpCR, assessed locally (central assessment will be performed at a later stage), bpCR, and ORR, the PK data, and the safety data collected till surgery, will be performed after the last patient has completed surgery. In this analysis, only the data collected till the day of surgery will be considered.

The final analysis will be performed after all patients have completed the 2-year follow-up period and will concern the evaluations of EFS and OS and the safety data collected during the entire study.

Since a single primary efficacy parameter is defined (tpCR assessed locally), and since the intermediate analysis will consider the assessment of this variable for all patients, no correction for multiplicity is required in the statistical testing.

9 DATA QUALITY CONTROL

Accurate and reliable data collection will be assured by verification and cross–check of the eCRF against the investigator's records by the study CRAs (Source Data Verification (SDV), by reviewing source documents for safety and compliance information (Source Data Review (SDR) and the maintenance of a drug–dispensing log by the investigator. Essential documents collection and maintenance will be reviewed through the investigator/institution Trial Master File (TMF).

Data for this study will be recorded via eCRF. It will be transcribed by the site from the source documents into the eCRF. Source-data verification will be risk based as described in the study monitoring conventions. Data queries requiring clarification are communicated to the site for resolution. Only authorised personnel will make corrections to the clinical database and an audit trail will document all corrections.

10 STUDY COMMITTEES – DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be implemented that reviews accumulating data of the clinical trial with respect to any potential safety issues, study progress and critical efficacy endpoints.
The DMC will be an independent board consisting of 2-3 physicians with special expertise in breast cancer. A physician is not allowed to participate in this clinical trial while serving on the DMC. The DMC will be supported by an independent statistician, if necessary.
The DMC will review only blinded safety and efficacy data of the clinical trial and support the interpretation of clinical trial results. During the trial, the DMC will be provided with SAE and SUSAR listings on a 6 monthly basis.
A DMC charter will be set up which defines the roles and responsibilities of the DMC.

11 ETHICAL ASPECTS

11.1 Declaration of Helsinki / Good Clinical Practice

The Declaration of Helsinki is the accepted basis for clinical study ethics, and must be fully followed and respected by all those engaged in research on human beings. Any exceptions must be justified and stated in the protocol. The latest version of the Declaration of Helsinki is available at www.wma.net.
Additionally it is the responsibility of all those engaged in research on human beings to ensure that the study is performed in accordance with the ”International Conference on Harmonisation” (ICH) international standards of Good Clinical Practice (ICH Harmonised Tripartite Guideline For Good Clinical Practice E6(R2) Current Step 4 version dated 9 November 2016)[33] and according to all applicable local Directives, laws and regulations concerning clinical studies.

11.2 Patient information and informed consent

It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study, after an adequate explanation of the aims, importance, anticipated benefits, potential hazards and consequences of the study according to applicable local laws. Written informed consent must be obtained before any study-specific procedures are performed. It must be also explained to the patient that they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason, without incurring any penalty or withholding of treatment on the part of the investigator.
With the declaration of consent, the patient agrees to the collection of data of his/her disease being recorded within the context of the clinical trial and that it may be transferred to the sponsor in pseudonymised form.
The subject/patient also agrees to allow the CRA/auditor/health authorities to verify the patient data collected against the subject’s/patient’s original medical records for source data verification.
The informed consent form personally signed and dated by the patient, or their legally authorized representative, must be kept on file by the investigator(s) and documented in the eCRF and the subject’s medical records. The investigator must confirm with the sponsor that he/she has obtained written informed consent.
If new safety information results in significant changes to the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue in the study.
If family doctors are to be informed of their patients’ participation in the clinical study, this should be mentioned in the consent form.

11.3 Independent ethics committees and regulatory authorities

11.3.1 Approval of the study by the regulatory authority and independent ethics committees

It is the responsibility of the sponsor to obtain and maintain independent approval from the applicable regulatory authority and a positive opinion from the competent ethics committees to

conduct the study in accordance with local legal requirements, statutes, and the European Clinical Trial Directive.
Indemnity insurance will be arranged for the trial subjects in accordance with the applicable local law.

11.3.2 Notification of the study

The sponsor is responsible for notifying the competent regional authority about the study and all principal investigators at the participating investigational sites, if applicable by local law.

11.3.3 Obligation to report and document

The sponsor and the investigator are responsible for complying with the requirements for reporting and documentation in accordance with local legal requirements and statutes.

12 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made via amendment. The sponsor is responsible for obtaining independent approval for substantial amendments from the applicable regulatory authority and a positive opinion from the competent ethics committees in accordance with local legal requirements, statutes, and the European Clinical Trial Directive. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects or when the changes are non-substantial and involve only logistical or administrative aspects of the trial (e.g. change of telephone numbers).

13 STUDY DOCUMENTATION, CRFS AND RECORD-KEEPING

13.1 Investigator's files / retention of documents

The investigator must maintain adequate and accurate records 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 two separate categories: investigator's study file and subject/patient data.

The investigator's study file will contain all essential documents such as the protocol/amendments, case report and query forms, patient information and informed consent form, ethics committee and regulatory authority approval, notification of the federal regulatory authority and competent regional authorities (if applicable), drug records, staff curriculum vitae and authorisation forms, and other appropriate documents/correspondence, etc.

Patient data includes patient hospital/clinic records (e.g. medical reports, surgery reports appointment book, medical records, pathology and laboratory reports, ECG, etc.), signed informed consent forms and patient screening and eligibility screening forms.

The investigator must keep these two categories of documents on file for as long as legally required by local and national regulations, or local IRB/ethics board policies whichever is longer, after completion or discontinuation of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in the event of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

All documents must be archived in a secure place and treated as confidential material.

13.2 Source documents and background data

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinical records. This is particularly important when case report forms are illegible or when errors in data transcription are suspected. In the event of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, as patient confidentiality is protected. According to the standards of the data protection law, all data obtained during a clinical study must be treated with discretion to guarantee the rights of the patient's privacy.

13.3 Audits and inspections

This study may be audited by the sponsor, any person authorised by the sponsor, or the competent health authority to determine the authenticity of the recorded data and compliance with the study protocol.

The investigator must be aware that source documents for this trial should be made available to appropriately qualified personnel working on behalf of the sponsor/auditor/health authority

inspectors after appropriate notification for the purposes of source data verification and proper review of the study progress. The verification of the case report form data must be done via direct inspection of the source documents. The investigator agrees to comply with the sponsor and regulatory authority requirements regarding the auditing of the study.
All materials used in clinical studies are subjected to quality control.

13.4 Case report forms

For each patient enrolled, an electronic case report form must be completed by the site investigator or an authorised delegate from the study team. If a patient withdraws from the study, the reason must be noted in the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to document the outcome clearly. No data recorded in the eCRF is to be considered as source. Sign-off for the patient data in the eCRF will be performed by the site investigator.

14 MONITORING THE STUDY

CRAs are responsible for familiarising the investigator(s) and the entire centre staff involved in the study with all study procedures, including the administration of the study drug.
A CRA will visit the study site before the first patient has been enrolled (initiation visit) to ensure the site is ready for patient enrolment. During the study the CRA will monitor the site as per the risk-based monitoring plan, which has been written to ensure patient safety and well-being, data quality and compliance with GCP, the TROIKA protocol, the applicable SOPs and the local regulations related to the conduct of clinical trials. Source Data Verification (SDV) and -Review (SDR) will be conducted, amongst other quality control techniques like e.g. investigator TMF review, subject enrolment follow-up and staff interviews, to ensure compliance. A CRA different from the one visiting the investigator's site will visit the pharmacy to ensure that study drug is being stored, dispensed, and accounted for according to specifications.
Key study personnel must be available to assist the CRA during these visits. The investigator (or his/her deputy) agrees to cooperate with the CRA to ensure that any issues detected during these monitoring visits are resolved.

15 CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator and the sponsor (or designated person) must ensure that all data obtained during a clinical study is treated with discretion to guarantee the rights of the patient's privacy, according to the standards of the data protection law. eCRFs or other documents should be submitted to the sponsor in pseudonymised form. The investigator should keep a patient identification log showing codes and names. The investigator should maintain documents not intended for submission to the sponsor, e.g. patients' written consent forms, in the strictest confidence.

16 STUDY REPORT AND PUBLICATION POLICY

This study will be entered into a clinical trial protocol registry and clinical results database. The sponsor is responsible for the timely reporting of study data. An integrated clinical study report (CSR) must be completed one year after the end of the study (whether completed or prematurely terminated). The report must be approved by the responsible specialist chosen by the sponsor, the project manager of the CRO, the statistician and the coordinating investigator by provision of their signatures. In this multi-centre study, the main publication will be a full publication of all data from all sites. Any publication of the results, either in part or in whole (abstracts in journals, oral presentations, etc.) by investigators or their representatives will require a pre-submission review by the sponsor and the coordinating investigator. The coordinating investigator will be given the choice to be the first or the last author for the main publication. The remaining positions will be based on recruitment, good data quality and scientific input to the study. The final author list will be a joint agreement between the coordinating investigator and the sponsor. For all other publications, the order of the authors will be determined according to recruitment, data quality and significant scientific input to the study, after consulting the coordinating investigator.

17 APPENDICES

Appendix 1: Adverse Event Categories for Determining Relationship to Test Drug
Appendix 2: ECOG Performance Status

17.1 Appendix 1 – Adverse Event Categories for Determining Relationship to Test Drug

(a) Related (must have one of them)

This category applies to those adverse events that are considered to be related to the test drug. An adverse event may be considered related if:

1. It follows a reasonable temporal sequence from administration of the drug
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject
3. It disappears or decreases on cessation or reduction in dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists: e.g. (1) bone marrow depression, (2) tardive dyskinesias.)
4. It follows a known pattern of response to the suspected drug
5. It reappears upon rechallenge

(b) Unrelated

This category is applicable to those adverse events which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under related.

17.2 Appendix 2 – ECOG Performance Status

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

18 REFERENCES

1. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-792.
2. Gasparini G, Gion M, Mariani L, et al. Randomized Phase II Trial of weekly paclitaxel alone versus trastuzumab plus weekly paclitaxel as first-line therapy of patients with Her-2 positive advanced breast cancer. Breast Cancer Res Treat. 2007;101(3):355-365.
3. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;23(19):4265-4274.
4. Ross JS, Fletcher JA, Linette GP, et al. The Her-2/neu gene and protein in breast cancer 2003: biomarker and target of therapy. Oncologist. 2003;8(4):307-325.
5. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659-1672.
6. Romond EH, Jeong JH, Rastogi P, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2012;30(31):3792-3799.
7. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-1283.
8. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005;23(16):3676-3685.
9. von Minckwitz G, Rezai M, Fasching PA, et al. Survival after adding capecitabine and trastuzumab to neoadjuvant anthracycline-taxane-based chemotherapy for primary breast cancer (GBG 40-GeparQuattro). Ann Oncol. 2014;25(1):81-89.
10. Untch M, Fasching PA, Konecny GE, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol. 2011;29(25):3351-3357.
11. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010;375(9712):377-384.
12. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. J Clin Oncol. 2010;28(1):92-98.

13. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v8-30.
14. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-1205.
15. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol. 2013;14(8):741-748.
16. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol. 2014;15(6):640-647.
17. Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol. 2011;12(3):236-244.
18. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164-172.
19. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2012;379(9816):633-640.
20. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17(6):791-800.
21. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(1):25-32.
22. Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol. 2012;13(9):869-878.
23. Jackisch C, Hegg R, Stroyakovskiy D, et al. HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016;62:62-75.
24. Buzdar AU, Suman VJ, Meric-Bernstam F, et al. Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): a randomised, controlled, phase 3 trial. Lancet Oncol. 2013;14(13):1317-1325.
25. Lammers P, Criscitiello C, Curigliano G, Jacobs I. Barriers to the Use of Trastuzumab for HER2+ Breast Cancer and the Potential Impact of Biosimilars: A Physician Survey in the United States and Emerging Markets. Pharmaceuticals (Basel). 2014;7(9):943-953.

26. McCamish M, Woollett G. Worldwide experience with biosimilar development. MAbs. 2011;3(2):209-217.
27. Rémuzat C, Dorey J, Cristeau O, Ionescu D, Radière G, Toumi M. Key drivers for market penetration of biosimilars in Europe. J Mark Access Health Policy. 2017;5(1):1272308.
28. Thill M. New frontiers in oncology: biosimilar monoclonal antibodies for the treatment of breast cancer. Expert Rev Anticancer Ther. 2015;15(3):331-338.
29. Giuliano AE, Connolly JL, Edge SB, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(4):290-303.
30. FDA/CDER (Food and Drug Administration/Center for Drug Evaluation and Research). Guidance for Industry: Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval. In:2014.
31. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006;24(19):3187-3205.
32. Stebbing J, Baranau Y, Baryash V, et al. CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial. Lancet Oncol. 2017;18(7):917-928.
33. ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E2(R6). Current Step 4 version dated 9 November 2016. 2016.
34. Gunter von Minckwitz, M.D., Marion Procter, Ph.D., Evandro de Azambuja, M.D., et al for the APHINITY Steering Committee and Investigators Adjuvant Pertuzumab and Trastuzumabin Early HER2-Positive Breast Cancer NEJM 2017 DOI: 10.1056/NEJMoa1703643