STATISTICAL ANALYSIS PLAN FOR THE FINAL ANALYSIS OF STUDY

EUDRACT # 2016-004019-11

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

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List of Abbreviations

β-HCG	Beta human chorionic gonadotropin
ADA	Anti-drug antibodies
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT (SGPT)	Alanine aminotransferase
ALC	Absolute Lymphocite Count
ANC	Absolute Neutrophil Count
AP	Alkaline phosphatase
aSAF	Adjuvant Safety Set
AST (SGOT)	Aspartate aminotransferase
ATEAE	Adjuvant Treatment Emergent Adverse Event
Bpm	Beats per minute
BSA	Body Surface Area
BUN	Blood urea nitrogen
bpCR	Breast pathological complete response
CI	Confidence interval
CISH	Chromogenic in-situ hybridization
CR	Complete response
CRA	Clinical research associate
CSR	Clinical Study Report
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
C_{trough}	Concentration of a drug observed after its administration and just prior to the administration of a subsequent dose
D	Day
DISH	Inform HER2 Dual ISH
EBC	Early breast cancer
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
EOT	End of treatment
FAS	Full Analysis Set
FISH	Fluorescent in-situ hybridization
FU	Follow-Up
GGT	Gamma-glutamyl transferase
HER2	Human Epidermal Growth Factor Receptor 2
ICH	International Council for Harmonization
IHC	Immunohistochemistry

ITT	Intention-to-treat
IWRS	Interactive web response system
kg	Kilogram
L	Liter
LLN	Lower limit of normal
LLOQ	Lower Limit of Quantification
LVEF	Left ventricular ejection fraction
m^2	Square meter (body surface area)
mFAS	modified Full Analysis Set
Mg	Milligram
min	Minute
mL	Milliliter
MedDRA	Medical Dictionary for Regulatory Activities
MUGA scan	Multigated acquisition angiogram scan
MRI	Magnetic resonance imaging
NAb	Neutralizing antibodies
NATEAE	Neo-Adjuvant Treatment Emergent Adverse Event
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetic
PPS	Per Protocol Set
PR	Partial response
PT	Preferred Term
PTAE	Post-treatment adverse event
PTAS	Post-Treatment Analysis Set
RBC	Red blood cell count
rPPS	restricted Per Protocol Set
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
tpCR	Total pathological complete response
ULN	Upper limit normal
WBC	White blood cell count

1. INTRODUCTION

In April 2019, the database was locked for the intermediate analysis before all data of the neo-adjuvant and surgery periods were entered, and before source data were verified and analyzed. At that time, the data on the surgery of 8 patients were not fully entered in the eCRF.

The analysis in April 2019 consisted of the analysis of the efficacy endpoints tpCR, bpCR, and response variables, the PK data, and the safety data collected till surgery.

Based on inspection by EMA (report GCP/2019/022), where the reliability of the data was questioned due to the premature database lock, a CAPA was raised and the database was unlocked by the sponsor for the neo-adjuvant and surgery period, to perform re-monitoring of this data and to re-lock the database after performing the necessary checks to ensure that the data were complete, accurate and consistent. This database re-lock took place in September 2020.

The purpose of the present Statistical Analysis Plan (SAP) is to precisely define the final statistical analysis of the data of the TROIKA study (EudraCT number 2016-004019-11). The SAP is based on Section 8 (Statistics) of the study protocol Version 3.0 (dated 1 October 2018). The SAP is prepared in compliance with ICH E9.

Any changes to the planned analyses occurring after finalization of the SAP will be described and justified in the Clinical Study Report (CSR).

2. SUMMARY OF THE PROTOCOL

2.1 Study Objectives

The primary objective of this Phase III 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 is assessed at the time of surgery after 8 cycles of neo-adjuvant treatment completion.

The secondary objectives of this study are:

- To compare 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®.

An ancillary study assessing the relationship between treatment effect defined by pCR status and GWAS analysis was planned and will be described in a separate analysis plan.

2.2 Study Design

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

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

Arm A:

- HD201 (Trastuzumab-biosimilar):
  - Cycle 1: 8 mg/kg IV loading dose over 90 minutes
  - Cycle 2: 6 mg/kg IV every 3 weeks over 60 minutes
  - Cycle 3 – 8: 6 mg/kg IV every 3 weeks over 30 minutes
  - Surgery,
  - Cycle 9: 8 mg/kg IV loading dose over 90 minutes
  - Cycles 10 – 18: adjuvant HD201 6 mg/kg over 30 minutes.
- Neo-adjuvant chemotherapy:
  - Cycles 1-4: Docetaxel 75 mg/m² on day 1 of each 3-weeks cycle via a 1h IV 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 IV infusion
    - Cyclophosphamide 500 mg/m² to be administered between 3-30 minutes via IV infusion

Arm B:

- Herceptin® (Trastuzumab): Same as Arm A
- Neo-adjuvant chemotherapy: Same as Arm A

It was planned to perform this study in 130 sites in approximately 21 countries.

Neo-adjuvant period

HD201/Herceptin® is 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® is not to be recalculated unless the body weight changes 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 is to be given. Subsequent maintenance HD201/Herceptin® doses of 6 mg/kg are then to be continued every 3 weeks.

Neo-adjuvant chemotherapy is administered immediately after HD201/Herceptin® infusion. Pre-treatment supportive medication including antiemetics is given according to institutional practice.

Surgery

After eight cycles of neo-adjuvant therapy, surgery is to be done within 3-8 weeks of the last dose of HD201/Herceptin®. Axillary lymph node dissection (ALND) was recommended. Lymph node axillary dissection must include the first and second level. Sentinel node biopsy is allowed as a possible therapeutic option in patients clinically node-negative 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.

After surgery, patients are to enter adjuvant period.

Adjuvant period

After surgery and depending on patient recuperation period, HD201/Herceptin® is to be administered as monotherapy at an IV 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 is to be given) 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 can receive hormonal therapy or radiotherapy or both. Treatment after the adjuvant period is to be determined according to the investigator's choice.

End of Treatment (EOT) Visit

All patients are to 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 are to be treated at the discretion of the investigator.

Post-treatment follow-up period

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

End of study was when the last patient had finalised the two-year post-treatment FU period.

2.3 Study Periods and Analyses

The study started in Q1 2018. The foreseen recruitment period was approximately 5 months in Asia and 6 months in Europe so that recruitment was to be completed by Q3 2018. End of study was when the last patient had finalized the two years post-treatment FU period. The primary endpoint was analysed in Q2 2019.

2.4 Arm Allocation and Blinding

All patients who fulfil the inclusion criteria and do not meet any exclusion criteria, were to be randomised centrally by IWRS in a ratio of 1:1 to either the HD201 arm or the Herceptin® arm. 500 patients were to be randomised. Each patient was assigned a unique randomisation number.

Patients were stratified by

- Geographical region (Asia, Eastern Europe, Central Europe, Western Europe).
- Clinical stage (stage II vs. III).
- Oestrogen and/or progesterone receptor status (positive vs. negative).

Patients were not permitted to be randomised more than once in the study.

Patients were randomised to receive HD201 or Herceptin® in a double-blind fashion such that neither the investigator nor the staff nor the patient nor the sponsor was to know which treatment was being administered.

HD201 and Herceptin® vials were presented in identical packaging boxes to ensure blinding of the study medication at the level of packaging. The HD201/Herceptin vials are slightly different in size. However, due to the identical labels affixed on the vials, the pharmacist preparing the infusion bags following reconstitution was only partially unblinded. The infusion bags were provided by the pharmacist to the investigator's site, and labelled identically, identified by a treatment number, patient number and cycle number, to ensure blinding of the investigator, the

staff, and the patient.

The team responsible for study supply and randomisation was only to reveal the treatment assignment to the trial team after database lock for the first intermediate analysis (i.e. after the last patient has completed surgery).

The pharmacist was to take all necessary measures not to provide access to the study medication packages/vials to the investigator nor the staff. The verification of the drug accountability logs, supplies, including partially used or empty vials and copies of the dispensing forms were 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, were to be used. Unblinding was only to be granted in case of an emergency.

A discussion with the sponsor or the sponsor's medical monitor was recommended before the patient was unblinded. If this was impractical, the investigator was to notify the sponsor as soon as possible, but without revealing the treatment assignment of the unblinded patient to the sponsor, unless that information was important for the safety of the patients currently in the study. The date and reason for unblinding was to be recorded in the eCRF.

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

2.5 Study Phases and Schedule of Assessments

The foreseen duration of each treatment cycle was 3 weeks and each treatment cycle was scheduled from the date of randomisation. Patients were to be treated with HD201/Herceptin® for a maximum of 18 cycles (8 neo-adjuvant; 10 adjuvant).

All patients were to 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 were treated at the discretion of the investigator.

After the EOT visit patients were to be followed every 6 months for an additional 2 years or until death, whichever occurred first. End of study was when the last patient had finalized the two-year FU period.

The following data collection time-points were foreseen:

- Screening: D-28 and D-7.
- Neo-adjuvant treatment period: Beginning (Day 1) of Cycle 1 to Cycle 8.
- End of neo-adjuvant treatment period: After Cycle 8.
- Before surgery: 3 to 8 weeks after last neo-adjuvant treatment.
- Surgery.
- Adjuvant period: 10 cycles.
- End of treatment: 4 weeks after last administration of study medication for patients completing the treatment period of 12 months and those discontinuing from the study.
- Follow-up: After the last administration of study medication patients were treated according to their physician's discretion. Patients were to be seen every 6 months after the EOT visit for a period of 2 years or until death, whichever occurred first, to collect data on cardiac safety (ECG/LVEF) and, for patients who underwent surgery, disease status (progression of disease, survival/death).

A window of ± 2 days applied to all visits and assessments, except for follow-up survival information collection which had a window of ± 7 days.

A flow-chart of assessments is given in the Appendix.

2.6 Sample Size

It was planned that 500 patients would be randomised to ensure completion of 450 patients (10% drop-out rate assumed). The sample size calculation was based on results from many randomised trials with data for tpCR. The following assumptions were made:

- The true difference in proportions of patients achieving tpCR is 0.00
- The proportion in the reference group is 0.40
- 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.

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 were to be randomised to ensure that sufficient patients complete the study without compromising the power of the study.

3. STUDY MEASURES

3.1 Data Recorded in the e-CRF

The following data will be considered for the analysis[1]:

3.1.1 Screening and Baseline Data

Demographic Data

- Date of birth, race (Asian, White/Caucasian, other), childbearing potential status (childbearing potential, surgical sterilization, peri-menopausal, postmenopausal for ≥ 2 years).

Medical and Surgical History

In case of medical or surgical history:

- Description.
- For disease: Date of onset (first diagnosis), ongoing at screening visit or end date, medical treatment ongoing at screening (yes, no).
- For surgery: Date of surgery.

Breast Cancer History

- Date first diagnosis.
- Breast(s) concerned.
- Clinical stage (0, 1A, IB, IIA, IIB, IIIA, IIIB, IIIC, IV, unknown/not done).
- Histological grade (I, II, III, unknown/not done).
- Differentiation (1, 2, 3, unknown/not done).
- Ploidy (1, 2, 3, unknown/not done).
- Proliferation (1, 2, 3, unknown/not done).
- Operable at screening (yes, no, unknown).
- Oestrogen receptor status (positive and % of cells, negative, unknown/not done).
- Progesteron receptor status (positive and % of cells, negative, unknown/not done).
- Breast cancer symptoms (yes, no) and if yes presence of inflammatory breast, breast pain, oedema arm(s), pain in arm(s), subfebrile status, other).

Imaging Examinations

- Chest scan (yes, no), and if yes: date, method (CT, MRI, other), result (normal, abnormal, description of abnormalities).
- Abdominal scan (yes, no), and if yes: date, method (CT, MRI, other), result (normal, abnormal, description of abnormalities).
- Isotope bone scan (yes, no), and if yes: date, result (normal, abnormal, description of abnormalities).
- Other examinations: date, method (CT, MRI, other), location, result (normal, abnormal, description of abnormalities).

Sentinel Node Biopsy

In case of sentinel nose biopsy:

- Date of biopsy.
- Number of nodes taken.
- Number of positive nodes.

[1] Whenever the selection 'other' is made the specification could also be entered.

HER2

Was a sample taken (yes, no). If no, reason, if yes:
- Date sample taken.
- HER2 status (positive, negative, unknown/not done).
- Immunohistochemistry (IHC) performed, and if performed, result (ICH0, ICH1+, ICH2+, ICH3+, not interpretable).
- Dual in situ hybridisation (DISH) performed to assess overexpression of HER2
- Fluorescence in situ hybridisation (FISH) performed, and if performed, result (positive, negative, not interpretable).
- Chromogenic in situ hybridisation (CISH) performed, and if performed, result (positive, negative, not interpretable).

3.1.2 Course of the Study

Visit Dates
- Screening.
- Cycles 1 to 8.
- Before surgery.
- Cycles 9 to 18.
- End of treatment.
- 6, 12, 18, 24 months follow-up.
- Unscheduled during neo-adjuvant treatment period, unscheduled during adjuvant treatment period, unscheduled during follow-up.

Study Drug Administration

Was study drug administered (yes, no). If no, reason, if yes:
- Type of dose ((re-)loading, maintenance).
- Number of vials used to prepare study drug, and for each vial the volume used (ml).
- Date of administration and start time and end time.
- Volume of infused bag (ml).
- Dose administered (mg/kg).
- Was all study medication administered (yes, no), and if no, volume administered (ml).
- In case of deviation from the administration as per protocol concerning dose, delay between administrations, or infusion time: Reason (AE, other).

Chemotherapy Administration

For docetaxel (Cycles 1 to 4), epirubicin (Cycles 5 to 8), and cyclophosphamide (Cycles 5 to 8):
- Date of administration and start time.
- Dose administered (mg).
- Administered as per package insert (yes, no), and if no, specification and reason (AE, other).

Concomitant Medications

For each medication:
- Generic name.
- Indication (medical/surgical history and reference to log, adverse event and reference to log, prophylaxis and specification).
- Dose.
- Unit.
- Frequency.
- Route.
- Start date and stop date, or ongoing.

Concomitant Non-Drug Therapy / Surgery

For each therapy or surgery:

- Description.
- Indication (medical/surgical history and reference to log, adverse event and reference to log, prophylaxis/other).
- Start date or date of surgery.
- For therapies stop date or ongoing at EOT visit.

End of Neo-Adjuvant Treatment Period

- Did the patient complete the neo-adjuvant treatment period (yes, no), and if no, reason(s) for premature discontinuation of neo-adjuvant treatment:
  - Disease progression (PD) and date of first PD.
  - Non-compliance.
  - Need of treatment with medication not allowed by the protocol.
  - Patient no longer consents to participate and explanation.
  - Intercurrent illness that interferes with study assessments and reference to the AE concerned.
  - Adverse event and reference to the AE concerned.
  - Investigator decision and explanation.
  - Pregnancy.
  - Termination of the study by the sponsor.
  - Lost to follow-up.
  - Death and date of death.
  - Other.
- Has the study treatment been unblinded (yes, no), and if yes, date, reason, and persons unblinded.
- Is the patient planned to undergo surgery (yes, no).

Surgery

- Was breast surgery performed (yes, no) and if yes, date, type (conservative, radical), description, and reason.

End of Adjuvant Treatment Period

- Did the patient complete the adjuvant treatment period (yes, no), and if no, reason(s) for premature discontinuation of adjuvant treatment:
  - Disease progression (PD) and date of first PD.
  - Non-compliance.
  - Need of treatment with medication not allowed by the protocol.
  - Patient no longer consents to participate and explanation.
  - Intercurrent illness that interferes with study assessments and reference to the AE concerned.
  - Adverse event and reference to the AE concerned.
  - Investigator decision and explanation.
  - Pregnancy.
  - Termination of the study by the sponsor.
  - Lost to follow-up.
  - Death and date of death.
  - Other.
- Has the study treatment been unblinded (yes, no), and if yes, date, reason, and persons unblinded.

End of Study

- Did the patient complete the follow-up period (24 months after completion of treatment) (yes, no), and if no:
  - Date of premature study discontinuation.
  - All reasons for premature study discontinuation:
    - Patient no longer consents to participate and explanation.
    - Adverse event and reference to the AE concerned.
    - Investigator decision and explanation.
    - Pregnancy.
    - Termination of the study by the sponsor.
    - Lost to follow-up.
    - Death and date of death.
    - Other and specification.

3.1.3 Efficacy Data

Clinical Tumour Assessment (Screening, Cycles 1 to 8, Before Surgery)

Was a clinical tumour assessment performed (yes, no). If no, reason, if yes:

- Date of clinical tumour assessment.
- Breast: Any lesion(s) (yes, no), and if yes:
  - Breast(s) concerned.
  - Location(s) (upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant, other).
  - Largest diameter (mm) or not measurable.
- Axillary lymph nodes: Lymph nodes involved (yes, no), and if yes:
  - Number of nodes.
  - Largest diameter (mm) or not measurable.
- For the assessments at the beginning of Cycles 1 to 8 and before surgery:
  - New lesions: any new lesion(s) (yes, no), and if yes:
  - Location(s) (breast, axillary lymph nodes) and specification.
  - Response:
    - Complete response (CR).
    - Partial response (PR).
    - Stable disease (SD).
    - Progressive disease (PD).
    - Not evaluable (NE).

Ultrasound (Screening, Before Surgery)

Was an ultrasound performed (yes, no). If no, reason, if yes:

- Date of ultrasound.
- Breast: Any lesion(s) (yes, no), and if yes:
  - Breast(s) concerned.
  - Location(s) (upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant, other).
  - Largest diameter (mm) or not measurable.
- Axillary lymph nodes: Lymph nodes involved (yes, no), and if yes:
  - Number of nodes.
  - Largest diameter (mm) or not measurable.
- For the assessment before surgery:
  - New lesions: any new lesion(s) (yes, no), and if yes:
  - Location(s) (breast, axillary lymph nodes) and specification.

- Response:
  - Complete response (CR).
  - Partial response (PR).
  - Stable disease (SD).
  - Progressive disease (PD).
  - Not evaluable (NE).

Mammography (Screening, Before Surgery)

Was a mammography performed (yes, no). If no, reason, if yes:

- Date of mammography.
- Any lesion(s) (yes, no) and if yes:
  - Breast(s) concerned.
  - Location(s) (upper outer, upper inner, lower outer, lower inner quadrant, other).
  - Largest diameter (mm) or not measurable.
- For the assessment before surgery:
  - New lesions: Any new lesion(s) (yes, no), and if yes, specification.
  - Response:
    - Complete response (CR).
    - Partial response (PR).
    - Stable disease (SD).
    - Progressive disease (PD).
    - Not evaluable (NE).

Other Tumour Assessment Breast/Axillary Lymph Nodes (Screening, Before Surgery)

Was another tumour assessment performed (yes, no). If no, reason, if yes:

- Date of other tumour assessment.
- Imaging technique.
- Breast: Any lesion(s) (yes, no), and if yes:
  - Breast(s) concerned.
  - Location(s) (upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant, other).
  - Largest diameter (mm) or not measurable.
- Axillary lymph nodes: Lymph nodes involved (yes, no), and if yes:
  - Number of nodes.
  - Largest diameter (mm) or not measurable.
- For the assessment before surgery:
  - New lesions: any new lesion(s) (yes, no), and if yes:
    - Location(s) (breast, axillary lymph nodes) and specification.
  - Response:
    - Complete response (CR).
    - Partial response (PR).
    - Stable disease (SD).
    - Progressive disease (PD).
    - Not evaluable (NE).

Overall Response at the End of the Neo-Adjuvant Treatment Period

- Date overall response documented.
- At end of neo-adjuvant treatment period:
  - Overall response:
    - Complete response (CR).
    - Partial response (PR).

- Stable disease (SD).
- Progressive disease (PD).
- Not evaluable (NE).

o Specification of progressive disease:
- Local recurrence/local progression.
- Other local recurrence/other local progression.
- Regional recurrence/regional progression.
- Contralateral invasive breast cancer.
- Distant recurrence/distant progression.

o In case of PD, cytological or histological confirmation (yes, no).

Pathological Findings During Surgery

- Breast
  - o Histological evidence of invasive tumour in the breast (yes, no), and if yes, was the tumour completely removed (yes, no), and largest diameter of the residual tumour (mm).
  - o Histological evidence of tumour bed (yes, no)
  - o In situ carcinoma in the breast (yes, no)
- Axillary lymph nodes
  - o Was axillary clearance performed (yes, no), and if yes, number of nodes removed, and number of nodes with residual tumour disease.

Disease Status after End of Treatment (6, 12, 18, 24 months Follow-up)

- Survival status (alive, dead, lost to follow-up), and in case patient died.
  - o Date of death.
  - o Main cause of death (disease progression, adverse event. Other and specification).
  - o Date of last contact.
- Does the patient have disease progression since the previous assessment (yes, no), and in case of progression:
  - o Date of first PD.
  - o Type of progressive disease:
    - Local recurrence/local progression.
    - Other local recurrence/other local progression.
    - Regional recurrence/regional progression.
    - Contralateral invasive breast cancer.
    - Distant recurrence/distant progression.

3.1.4 Safety Data

Adverse Events (till 7 months after end of treatment)

For each adverse event the following data are collected:

- Adverse event.
- Severity (NCI-CTCAE grade 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), 5 (fatal).
- Start date and start time.
- Outcome (recovered and date recovered, recovered with sequelae and date recovered with sequelae, fatal and date of death, not recovered and date of last assessment, unknown).
- Serious (yes, no).
- Relationship with study drug (definitely related, probably related, possibly related, unlikely related, unrelated, not applicable).
- Relationship with chemotherapy (definitely related, probably related, possibly related,

unlikely related, unrelated, not applicable).
- Action taken with study drug (none, drug withdrawn, drug reduced, drug delayed, drug interrupted, infusion time prolonged, dose increased, not applicable, other action taken).
- Treatment (yes, no) and type of treatment (medical, surgical, non-drug therapy).

Laboratory Data
- For haematology and clinical chemistry: date sample taken and laboratory.
- Haematology [red blood cell count (RBC), haemoglobin, haematocrit, white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), platelet count], and clinical chemistry [total bilirubin, serum creatinine, total protein, albumin, BUN/urea, sodium, potassium, calcium, alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT)], assessed at the following time-points:
  - Screening: Within 7 days prior to the first infusion.
  - Cycles 1 to 8: Within 2 days prior to each study drug administration.
  - Before surgery.
  - Cycles 9, 14, and 18: Within 2 days prior to each study drug administration.
  - Other cycles: At the discretion of the investigator.
  - End of treatment.

  The value of each test is recorded, the unit, lower and upper limit of the normal range, whether it is within the normal range, and if not, whether it is clinically significant.
- Pregnancy testing (Within 7 days prior to start of treatment, before Cycles 1 to 8, before surgery, before cycles 9 to 18)
  - Method (serum β-HCG, urine dipstick, other).
  - Date of test.
  - Result (negative, positive, not available).

Physical Examination (Screening, Cycles 1 to 8, Before Surgery, Cycles 9 to 18, End of Treatment, 6, 12, 18, and 24 months after end of treatment visit)
- Was a physical examination performed (yes, no), and if yes: Where there any abnormal findings (yes, no) and if yes, description of abnormalities (other than breast disease).

Vital Signs (Screening, Cycles 1 to 8, Before Surgery, Cycles 9 to 18, End of Treatment, 6, 12, 18, and 24 months after end of treatment visit)
- Body height (cm).
- Body weight (kg).
- Calculated BSA (Dubois and DuBois) (m^2) (only on cycles with chemotherapy).
- BSA used to calculate chemotherapy dosage (m^2).
- Systolic and diastolic blood pressure (mmHg).
- Pulse rate (bpm).
- Body temperature (°C).
- ECOG Performance Status (0, 1, 2, 3, 4, not done).

12-lead ECG (Screening, Cycle 5, Before Surgery, Cycles 12 and 16, End of Treatment, 6 and 12 months after end of treatment visit)
- Date of assessment.
- Overall interpretation (normal, abnormal not clinically significant, abnormal clinically significant).
- In case of abnormal result: Description.

Left Ventricular Ejection Fraction (LVEF) (Screening, Cycle 5, Before Surgery, Cycles 12 and 16, End of Treatment, 6 and 12 months after end of treatment visit)

- Date of assessment.
- LVEF (%).
- Lower limit normal (%).
- Method (ECHO, MUGA, other).

Immunogenicity Sampling (Screening, Before Cycle 5, Before Surgery, After surgery before Cycle 10, Before Cycle 14, End of Treatment, 12 months after end of treatment visit)

- Date sample taken.
- Human trastuzumab antibodies status obtained from the central laboratory: Negative/Positive (Screening result, Confirmatory Result HD201, Confirmatory Result Herceptin, Final ADA Result).

Note: The sample before Cycle 5 was only to be tested in case the pre-surgery sample was ADA positive.

Prior and Concomitant Medications (till end of treatment visit)

For each medication:

- Generic name.
- Indication (medical/surgical history and reference to log, adverse event and reference to log, prophylaxis and specification).
- Dose.
- Unit.
- Frequency.
- Route.
- Start date.
- Stop date or ongoing at EOT visit.

Concomitant Non-Drug Therapy / Surgery (till end of treatment visit)

For each therapy or surgery:

- Description.
- Indication (medical/surgical history and reference to log, adverse event and reference to log, prophylaxis/other).
- Start date or date of surgery.
- For therapies stop date or ongoing at EOT visit.

Anti-Cancer Treatment during the Adjuvant Treatment Period

For each hormonal therapy:

- Specification.
- Start date and stop date or ongoing at EOT visit.

For each radiotherapy:

- Location of irradiation.
- Start date and stop date or ongoing at EOT visit.

3.1.5 Pharmacokinetic Data

For each patient of the HD201 group, separately for Cycles 5, 8, 10 and 14:

- Vial numbers used to prepare the study drug administered (data from eCRF).
- Batch numbers of the vials.
- Production process for each batch.
- Date and time sample taken.
- Trough value (C_{trough}).
- Number of days between administration of study drug at the previous cycle and sample taken for C_{trough}:
  Date of C_{trough} sample – Date of administration of study drug at the previous cycle.

Blood samples for PK analysis of study medication are taken in all patients pre-infusion at the start of Cycles 5, 8, 10 and 14. The samples were submitted for analysis to a central laboratory. For the statistical analysis, values below the lower limit of quantification (LLOQ) are replaced by LLOQ/2.

PK results will only be considered for the analysis if documented on scheduled visits, and if the PK sample was taken before study drug administration on that cycle. An analysis was performed based on all samples and on samples taken within 19 to 23 days after the study drug administration on the previous cycle.

The analysis will be performed on the modified Full Analysis Set (mFAS) and on the Per Protocol Set (PPS).

3.2 Derived Variables

3.2.1 Description at Screening

- Geographical region:
  - Asia: Malaysia, Philippines, Republic of Korea, Thailand
  - Western Europe: Belgium, France, Italy, The Netherlands, Spain, Germany
  - Central Europe: Bulgaria, Czech Republic, Estonia, Hungary, Poland
  - Eastern Europe: Belarus, Georgia, Russian Federation, Ukraine

  Since only few patients were enrolled in Central Europe, Central Europe will be pooled with Western Europe in the analyses adjusted for stratification factors.
- Age (year) = (date of informed consent – date of birth)/365.25.
- Age category based on the date of birth and the date of informed consent (as used in everyday language):
  - < 18 years
  - ≥ 18 and < 65 years
  - ≥ 65 and < 75 years
  - ≥ 75 years
- Time since first diagnosis (month)
  = 12 x (informed consent – date of first diagnosis)/365.25.
- Medical history terms are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 21.0. Each Preferred Term (PT) will be associated with its primary System Organ Class (SOC).
- Estrogen/Progesterone status:
  - Positive: Estrogen status or Progesterone status = Positive
  - Negative: Estrogen status and Progesterone status = Negative
- Tumour Assessments:
  - Breast largest diameter category: < 10 mm, 10 – 30 mm, > 30 mm
  - Nodes category: 0 nodes, 1-3 nodes, > 3 nodes

3.2.2 Course of the Study

Entire study

- Date study termination = last of (dates of study visits and date of premature discontinuation)
- Study duration (week) =
  (date of last study visit or premature discontinuation – date of informed consent)/7.

Study drug exposure during the neo-adjuvant phase

- Treatment duration (week) =
  (date of last administration in the neo-adjuvant phase–date of first administration+21)/7.
- Cumulative dose administered (mg/kg) = sum of all actual doses administered during Cycles 1 to 8.
- Dose Intensity (mg/kg/week) =
  Cumulative dose administered (mg/kg) / treatment duration (week).
- Planned Dose Intensity (mg/kg/week) =
  [8 (mg/kg) + 7 * 6 (mg/kg)] / (8 * 3 weeks) = 2.083 (mg/kg/week).
- Relative dose intensity (%) =
  100 x Dose Intensity (mg/kg/week) / Planned Dose Intensity.

- Relative dose intensity class:
  - …
  - >= 70% - < 80%
  - >= 80% - < 90%
  - >= 90% - <= 110%
  - > 110% - <= 120%
  - …

Study drug exposure during the adjuvant phase

- Treatment duration (week) =
  (date of last administration–date of first administration during the adjuvant phase+21))/7.
- Cumulative dose administered (mg/kg) = sum of all actual doses administered during Cycles 9 to 18.
- Dose Intensity (mg/kg/week) =
  Cumulative dose administered (mg/kg) / treatment duration (week).
- Planned Dose Intensity (mg/kg/week) =
  [8 (mg/kg) + 9 * 6 (mg/kg)] / (10 * 3 weeks) = 2.067 (mg/kg/week).
- Relative dose intensity (%) =
  100 x Dose Intensity (mg/kg/week) / Planned Dose Intensity.
- Relative dose intensity class:
  - …
  - >= 70% - < 80%
  - >= 80% - < 90%
  - >= 90% - <= 110%
  - > 110% - <= 120%
  - …

Study drug exposure during the entire treatment period

- Duration of exposure (week) =
  (date of last administration–date of first administration+21))/7.
- Duration of exposure category:
  - <= 12 weeks
  - > 12 weeks - <= 24 weeks
  - > 24 weeks - <= 36 weeks
  - > 36 weeks - <= 48 weeks
  - > 48 weeks - <= 54 weeks
  - > 54 weeks - <= 60 weeks
  - > 60 weeks - <= 66 weeks
  - > 66 weeks.
- Cumulative dose administered (mg/kg) = sum of all actual doses administered during Cycles 1 to 18.

Post-treatment follow-up period

- Duration of post-treatment follow-up period (week) = (date of last study visit after EOT visit or premature discontinuation during follow-up – date of EOT visit)/7.
  If the EOT visit was not performed, the date of EOT will be estimated by the date of the last administration of study drug + 28 days.

3.2.3 Efficacy Data

Total pathological complete response (tpCR) local reading

tpCR is achieved if the following applies:

- Breast: Histological evidence of invasive tumour in the breast (yes, no) is answered 'No'.
  OR
- Breast: Histological evidence of invasive tumour in the breast (yes, no) is answered 'Yes' and 'Largest diameter of the residual tumour' is zero.

AND, if previous condition is fulfilled,

- Axillary lymph nodes: Was axillary clearance performed (yes, no) is answered 'Yes', and 'Number of nodes with residual tumour disease' is zero.
  OR
- Axillary lymph nodes: Was axillary clearance performed (yes, no) is answered 'No', and 'Was a sentinel node biopsy performed' (at screening) is answered 'Yes' with zero 'Number of positive nodes'.

In case 'Was axillary clearance performed is answered 'Yes', and 'Number of nodes with residual tumour disease' is zero and 'Was a sentinel node biopsy performed' (at screening) is answered 'Yes', with number of positive nodes larger than zero, the patient is considered to be a non-responder.

A patient who did not undergo surgery due to lack of efficacy (i.e. had progressive disease at end of the neo-adjuvant treatment period or before surgery) is considered to be a non-responder.

Total pathological complete response (tpCR) central reading

Based on results on Breast Pathological Complete Response and Lymph Nodes Invasion as provided by sponsor.

tpCR is achieved when:

- Breast Pathological Complete Response = Yes
- Lymph Nodes Invasion = No

tpCR is not achieved when both bpCR and Lymph Nodes Invasion not missing and:

- Breast Pathological Complete Response = No
- Lymph Nodes Invasion = Yes

Breast pathological complete response (bpCR) local reading

bpCR is achieved if the following applies:

- Breast: Histological evidence of invasive tumour in the breast (yes, no) is answered 'No'.
  OR
- Breast: Histological evidence of invasive tumour in the breast (yes, no) is answered 'Yes' and 'Largest diameter of the residual tumour' is zero.

A patient who did not undergo surgery due to lack of efficacy is considered to be a non-responder.

Breast pathological complete response (bpCR) central reading

Result on Breast Pathological Complete Response and Lymph Nodes Invasion provided by the sponsor.

Overall Response

Overall Response is defined based on the assessment at the end of the neo-adjuvant treatment period.

Response (Regrouped)

For statistical testing, response of CR or PR are regrouped. If a patient did not undergo surgery due to lack of efficacy, or the assessment is missing or NE (not evaluable) regrouped response is considered to be 'No'.

Event-Free Survival (EFS)

EFS is defined as the time between randomization and the first of any of the following events:

- Progression of disease (also in case PD occurred before surgery)
- Local or distant recurrence
- Second primary cancer (as captured in the adverse events log of the database)
- Death due to any cause.

Patients without the event are censored on the date last known to be alive.

In a sensitivity analysis the observation period will be limited to the last of the scheduled visits that occurred without interruption. If a scheduled visit was replaced by a phone contact this is also considered to be a scheduled visit. For this analysis a visit/contact is considered missing if it took place more than 30 days after the scheduled date. If an event occurred within the period between the last scheduled visit and the next foreseen scheduled visit the observation period is extended till that occurrence.

Overall Survival (OS)

OS is defined as the time between randomization and time of death from any cause. Patients who did not die during the study are censored on the date last known to be alive.

3.2.4 Safety Data

Adverse events

- Adverse events are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 21.0. Each Preferred Term (PT) will be associated with its primary System Organ Class (SOC).
- Relationship of adverse events to study drug:
  - Related: Assessed as definitely related, probably related, possibly related, or relationship assessment missing.
  - Unrelated: Assessed as unlikely related or unrelated.
- Relationship of adverse events to chemotherapy:
  - Related: Assessed as definitely related, probably related, possibly related, , or relationship assessment missing.
  - Unrelated: Assessed as unlikely related or unrelated.
- Pre-treatment adverse event is an adverse event starting before the beginning of the first administration of study medication and not worsening on or after the first administration of study medication.
- Neo-adjuvant treatment-emergent adverse event (NATEAE):
  Adverse events starting or worsening on or after the first administration of neo-adjuvant study medication and:
  - If adjuvant study treatment was administered:
    start date < date of first administration of adjuvant study medication.
  - If no adjuvant study treatment was administered and surgery took place:
    start date < date of surgery + 30 days.
  - If no adjuvant study treatment was administered and surgery did not take place:
    start date < date of last administration of neo-adjuvant study medication + 30 days.

- Adjuvant treatment-emergent adverse event (ATEAE):
  Adverse event starting or worsening on or after the first administration of adjuvant study medication and:
  - If an end of treatment (EOT) visit took place:
    start date < date of EOT visit
  - If no EOT visit took place:
    start date < date of last administration of adjuvant study medication + 30 days.
- Treatment-emergent adverse event (TEAE):
  Adverse event starting or worsening on or after the first administration of neo-adjuvant study medication and:
  - If adjuvant study treatment was administered and an EOT visit took place:
    start date < date of EOT visit
  - If adjuvant study treatment was administered and no EOT visit took place:
    start date < date of last administration of adjuvant study medication + 30 days.
  - If no adjuvant study treatment was administered and surgery took place:
    start date < date of surgery + 30 days.
  - If no adjuvant study treatment was administered and surgery did not take place:
    start date < date of last administration of neo-adjuvant study medication + 30 days.
- Post-treatment adverse event (PTAE):
  - Adverse event starting or worsening on or after the first administration of study medication
  - Not classified as TEAE
  - Start date ≤ date of last administration of treatment + 7 months (214 days).
- Adverse events of special interest:
  - Cardiotoxicity identified as adverse events with:
    - MedDRA SMQ 'Cardiac failure'
    - MedDRA SMQ 'Cardiomyopathy'
    - All MedDRA SMQs under the MedDRA SMQ 'Cardiac arrhythmias'
      - MedDRA SMQ 'Arrhythmia related investigations, signs and symptoms'
      - MedDRA SMQ 'Congenital and neonatal arrhythmias'
      - MedDRA SMQ 'Cardiac arrhythmia terms, nonspecific'
      - MedDRA SMQ 'Conduction defects'
      - MedDRA SMQ 'Disorders of sinus node function'
      - MedDRA SMQ 'Bradyarrhythmia terms, nonspecific'
      - MedDRA SMQ 'Supraventricular tachyarrhythmias'
      - MedDRA SMQ 'Ventricular tachyarrhythmias'
      - MedDRA SMQ 'Ttachyarrhythmias terms, nonspecific'.
    - MedDRA PT 'Left ventricular hypertrophy'.
  - Infusion-site reactions and hypersensitivity identified as adverse events with:
    - MedDRA SMQ 'Hypersensitivity'
    - MedDRA PT 'Acute respiratory distress syndrome'
    - MedDRA PT 'Allergic respiratory disease'
    - MedDRA PT 'Bronchospasm'
    - MedDRA PT 'Chills'
    - MedDRA PT 'Dyspnoea'
    - MedDRA PT 'Dyspnoea at rest'
    - MedDRA PT 'Headache'
    - MedDRA PT 'Hyperpyrexia'

- MedDRA PT 'Hypotension'
- MedDRA PT 'Nausea'
- MedDRA PT 'Oxygen saturation abnormal'
- MedDRA PT 'Oxygen saturation decreased'
- MedDRA PT 'Pyrexia'
- MedDRA PT 'Rash'
- All MedDRA PTs containing 'Rash'
- MedDRA PT 'Respiratory distress'
- MedDRA PT 'Tachycardia'
- MedDRA PT 'Vomiting'
- MedDRA PT 'Wheezing'.

o Haematotoxicity identified as adverse events with:
- All MedDRA SMQs under the MedDRA SMQ 'Haematopoietic cytopenias'
  - MedDRA SMQ 'Haematopoietic cytopenias affecting more than one type of blood cell'
  - MedDRA SMQ 'Haematopoietic erythropenia'
  - MedDRA SMQ 'Haematopoietic leukopenia'
  - MedDRA SMQ 'Haematopoietic thrombocytopenia'.

o Oligohydramnios identified as adverse events with:
- MedDRA PT 'Oligohydramnios'.

o Pulmonary disorders identified as adverse events with:
- MedDRA SMQ 'Interstitial lung disease'
- MedDRA SMQ 'Pulmonary hypertension'
- MedDRA PT 'Pleural effusion'
- MedDRA PT 'Respiratory distress'
- MedDRA PT 'Acute pulmonary oedema'
- MedDRA SMQ 'Respiratory failure'.

o Infections identified as adverse events with:
- MedDRA SOC 'Infections and infestations'.

Laboratory data

- CTCAE (Version 4.03) severity grades for selected haematology and chemistry parameters are given in Table 1. For laboratory variables for which there is a bidirectional grade (ALC, calcium, sodium, potassium), separate grading is performed for low and high values. For low values a grade of 0 is given for all values above or at the lower limit of the normal range. For high values a grade of 0 is given for all values below or at the upper limit of normal range, except for lymphocytes for which 4 10^9/L is the upper limit for grade 0.
- Status for the other haematology and chemistry variables:
  - o Below lower limit normal range (LLN)
  - o Within normal range
  - o Above upper limit normal range (ULN).

Table 1 - CTCAE Severity Criteria for Clinical Laboratory Tests

Hematology	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	≥10.0 g/dL to < LLN	≥8.0 to <10.0 g/dL	<8.0 g/dL	
Platelet count	≥75×10^9/L to <LLN	≥50 to <75×10^9/L	≥25 to <50×10^9/L	<25×10^9/L
WBC count	≥3×10^9/L to <LLN	≥2 to <3×10^9/L	≥1 to <2×10^9/L	<1×10^9/L
Neutrophils (ANC)	≥1.5×10^9/L to <LLN	≥1 to <1.5×10^9/L	≥0.5 to <1×10^9/L	<0.5×10^9/L
Lymphocytes (ALC)	≥0.8×10^9/L to <LLN	≥0.5 to <0.8×10^9/L or >4 to ≤20×10^9/L	≥0.2 to <0.5×10^9/L or >20×10^9/L	<0.2×10^9/L
Chemistry	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Albumin	<LLN to 30 g/L	<30 – 20 g/L	<20 g/L	
Calcium	>ULN to ≤2.9 mmol/L or ≥2.0 mmol/L to <LLN	>2.9 to ≤3.1 mmol/L or ≥1.75 to <2.0 mml/L	>3.1 to ≤3.4 mmol/L or ≥1.5 to <1.75 mmol/L	>3.4 mmol/L or <1.5 mmol/L
OR				
Ionized Calcium	>ULN to ≤1.5 mmol/L or ≥1.0 mmol/L to <LLN	>1.5 to ≤1.6 mmol/L or ≥0.9 to <1.0 mml/L	>1.6 to ≤1.8 mmol/L or ≥0.8 to <0.9 mmol/L	>1.8 mmol/L or <0.8 mmol/L
Sodium	>ULN to ≤150 mmol/L or ≥130 mmol/L to <LLN	>150 to ≤155 mmol/L	>155 to ≤160 mmol/L or ≥120 to <130 mmol/L	>160 mmol/L or <120 mmol/L
Potassium	>ULN to ≤5.5 mmol/L or ≥3.0 mmol/L to <LLN	>5.5 to ≤6.0 mmol/L	>6.0 to ≤7.0 mmol/L or ≥2.5 to <3.0 mmol/L	>7.0 mmol/L or <2.5 mmol/L
Creatinine	>ULN to ≤1.5×ULN	>1.5 to ≤3.0xULN	>3.0 to ≤6.0xULN	>6.0xULN
AST (SGOT)	>ULN to ≤3×ULN	>3 to ≤5×ULN	>5 to ≤20×ULN	>20×ULN
ALT (SGPT)	>ULN to ≤3×ULN	>3 to ≤5×ULN	>5 to ≤20×ULN	>20×ULN
Alk. phosphatase	>ULN to ≤2.5×ULN	>2.5 to ≤5.0×ULN	>5.0 to ≤20.0×ULN	>20.0×ULN
GGT	>ULN to ≤2.5×ULN	>2.5 to ≤5.0×ULN	>5.0 to ≤20.0×ULN	>20.0×ULN
Total bilirubin	>ULN to ≤1.5×ULN	>1.5 to ≤3.0×ULN	>3.0 to ≤10.0×ULN	>10.0×ULN

AST (SGOT)=aspartate aminotransferase; ALT (SGPT)=alanine aminotransferase.

LLN=lower limit of normal range; ULN=upper limit of normal range

NOTE: Some grades can be impossible depending on LLN and ULN (e.g. if LLN for neutrophils = 1.5 x 10^9). For the affected parameters grades will be grouped.

Immunogenicity

- Status of human anti-trastuzumab antibodies:
  - Positive: If 'Confirmatory Result' is positive
  - Negative:
    - If 'Confirmatory Result' is negative
    - If 'Confirmatory Result' is missing and 'baseline Result' is negative

  Worst status after baseline: positive if any ADA result after baseline is positive
- Status of neutralizing antibodies (Nab) for all ADA positive results.

Prior and Concomitant Medications and Non-Drug Therapy/Surgery

Prior and concomitant medications and anti-cancer treatment during the adjuvant treatment period, will be coded using the WHO-DRUG dictionary, version December 2011 at the level of the ATC code. ATC codes are attributed taking indication and route of administration into account.

The following definitions are used to determine the periods of use of medication and non-drug therapy/surgery:

- Prior medication and non-drug therapy/surgery:
  Start date before the day of first neo-adjuvant study drug administration
- Concomitant medication and non-drug therapy/surgery during the neo-adjuvant phase
  Ongoing at the first administration of neo-adjuvant study medication
  OR
  Start date on or after the first administration of neo-adjuvant study medication and:
  - If adjuvant study treatment was administered:
    start date < date of first administration of adjuvant study medication.
  - If no adjuvant study treatment was administered and surgery took place:
    start date < date of surgery + 30 days.
  - If no adjuvant study treatment was administered and surgery did not take place:
    start date < date of last administration of neo-adjuvant study medication + 30 days.
- Concomitant medications and non-drug therapy/surgery during the adjuvant phase:
  Ongoing at the first administration of adjuvant study medication
  OR
  Start date on or after the first administration of adjuvant study medication and:
  - If an EOT visit took place: start date < date of EOT visit
  - If no EOT visit took place:
    start date < date of last administration of adjuvant study medication + 30 days.

3.2.5 Sample Description

- Reason for not undergoing surgery:
    - For patients who did not complete the neo-adjuvant treatment period: Reason for not completing this period.
    - For patients who completed the neo-adjuvant treatment period: Reason for not performing surgery.
    - For patients who completed the neo-adjuvant treatment period but for whom no surgery was planned: Reason for not planning surgery (as derived from comment field).
    - For patients for whom it is not known whether they completed the neo-adjuvant treatment period and for whom it is not known whether surgery is performed: "Not known upon database lock for primary efficacy analysis".

4. ANALYSIS SETS AND SUBGROUPS

The following analysis sets will be considered for the analysis:

Total Set:	All patients who consented to participate in the study.
Full Analysis Set (FAS):	All randomised patients.
modified FAS (mFAS):	All randomised patients who received at least one dose of study medication (HD201 or Herceptin®).
Per Protocol Set (PPS):	All patients of the mFAS who received neo-adjuvant study medication according to the protocol, without any major protocol deviation impacting the primary efficacy assessment, and who had surgery after completion of neo-adjuvant treatment or did not undergo surgery due to lack of efficacy. Protocol deviations will be assessed during a pre-analysis review meeting that will be held before database lock.

Note: The PPS was determined during the blind review meeting of 21/04/2019 and has been maintained for the analyses described in this SAP.

restricted PPS (rPPS):	All patients of the PPS excluding: - Patients with sentinel node biopsy procedure and positive nodes at screening. - Patients without residual breast tumour, without axillary clearance, and without sentinel node biopsy performed at screening.
Safety Set (SAF):	All patients of the FAS who received at least one dose of neo-adjuvant study medication (HD201 or Herceptin®).
Adjuvant Safety Set (aSAF):	All patients of the FAS who received at least one dose of adjuvant study medication (HD201 or Herceptin®).

Post-Treatment Analysis Set (PTAS): All patients of the FAS with available data for the post-treatment follow-up period.

For the analyses based on the mFAS, patients will be classified according to the treatment assigned at randomisation. For the analyses based on the SAF, the aSAF, the PTAS, and the PPS and restricted PPS, patients will be assigned as treated.

The exclusion of patients from the analysis sets will be discussed during data review meetings that will be held before database lock.

For the populations SAF, mFAS, PPS and rPPS the following additional subgroups were considered for the analysis:

- Patients having a valid result for tpCR central reading
- Patients having a valid result for bpCR central reading.

The analyses of the demographic data and patient characteristics will be performed on the SAF/mFAS, aSAF, PPS, rPPS and all subgroups.

The efficacy analyses will be performed for the PPS and mFAS. The primary set for the analysis is the PPS. Supportive analyss of locally and centrally assessed tpCR and bpCR will be performed on the rPPS, the PPS excluding the Italian sites and the PPS restricted to countries with at least 10 patients.

Analysis of the response variables is performed on the SAF/mFAS, PPS, rPPS, PPS excluding the Italian sites, PPS excluding patients with inflammatory breast cancer and PPS for each country with at least 10 patients.

The analyses of the pharmacokinetic data will primarily be performed on the basis of the PPS and supportively on the basis of the mFAS.

The analysis of adverse events will be performed on the SAF for the neo-adjuvant period and the entire treatment period, on the aSAF for the adjuvant treatment period, and on the PTAS for the post-treatment follow-up period.

The analyses of the other safety data will be performed on the SAF.

5. STATISTICAL METHODOLOGY

5.1 Statistical Methods and Models

The descriptive statistical analysis will consist of:

- Summary statistics for quantitative variables including the mean, standard deviation, 95% CI of the mean, minimum, Q1, median, Q3, maximum, number of observations, and number of missing values.
- For the time to event variables EFS, sensitivity analysis of EFS, and OS: Kaplan-Meier survival analysis to estimate the median time and 95% CI and the rate at 2 years after the end of treatment and 95% CI.
- For categorical variables counts and percentages will be calculated for all values or categories among the patients with available data. For key categorical variables exact 95% Clopper-Pearson confidence intervals (CI) will be presented for each treatment group.

Note: For demographic data and baseline characteristics and for safety variables, the analyses described in this document will be descriptive and consist of summary statistics for each treatment group. No statistical tests or models will be used to compare the treatment groups.

The inferential statistical analysis will consist of:

- For tpCR and bpCR assessed by both local reading and central reading, overall response, mammography response, ultrasound response, clinical response:
    - Difference of the frequency of responders in the 2 treatment groups with exact 95% Santner-Snell CI.
    - Ratio of the frequency of responders in the 2 treatment groups with 95% CI based on normal approximation.
    - For tpCR, equivalence testing by comparing the exact 95% Santner-Snell CI on the difference between the 2 treatment groups with the interval [-0.15; +0.15].
    - Fisher Exact test comparing the 2 treatment groups.
    - Logistic regression model comparing the 2 treatment groups adjusting for region, stage, and E2/P4 receptor status: Adjusted difference and ratio and corresponding 95% CI and the p-value for the effect of treatment.

      NOTE: The logistic regression analysis for the model-based estimation of risk difference and risk ratio was performed using two different approaches. A first approach is based on the SAS procedure PROC NLMIXED (referred to as NLMIXED). This type of models is known to be unstable, with small changes in the input leading to important changes in the output. A second approach was introduced based on the SAS procedure PROC GENMOD in combination with PROC LOGISTIC (referred to as GENMOD), which is a combination of logistic, binomial and log-binomial regression. This model proved to be more stable, and therefore provides more reliable results.
- For EFS and sensitivity analysis of EFS:
    - Kaplan-Meier analysis and log-rank test to compare the two treatment groups and the relationship with tpCR and bpCR.
    - Cox proportional hazards regression to evaluate the effect of treatment. region, stage, E2/P4 receptor status, and the relationship with tpCR and bpCR.

- For OS:
    - Kaplan-Meier analysis and log-rank test to compare the two treatment groups.

- For C_{trough} at Cycle 5, 8, 10 and 14:
    - Difference of the mean C_{trough} in the 2 treatment groups with 90% CI.
    - Equivalence testing by comparing the 90% CI on the difference between the 2 treatment groups with the interval [-20%; +20%].
    - Equivalence testing by comparing the 90% CI on the geometric mean ratio between the 2 treatment groups with the interval [80%; 125%].

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

All individual data considered in the analysis will be listed.

5.2 Statistical Software

The statistical analysis will be performed using the SAS (Statistical Analysis System) software for WINDOWS, Version 9.4.

5.3 Definitions

The neo-adjuvant baseline value is the last available value before onset of study treatment. The adjuvant baseline value is the value at the start of adjuvant treatment (Cycle 9).

The change from neo-adjuvant baseline and from adjuvant baseline will be calculated as the value at a visit minus the value at baseline.

5.4 Missing Data

Missing or partial dates will be imputed as follows:

- For date of birth, if the day is missing, but not the month and year, the day will be imputed to 15. If the day and month are missing, but not the year, the day and month will be imputed to 1 July. If the date is completely missing, no imputation will be performed.
- For date of first diagnosis, if the day is missing, but not the month and the year, the day will be imputed to the first day of the month. If the day and month are missing, but not the year, the day and month of diagnosis will be imputed to 1 January. If the date is completely missing, no imputation will be performed.
- For partial or missing start date of concomitant medications and anti-cancer treatment during the adjuvant treatment period it will be assumed that the treatment was started prior to the first administration of study medication (neo-adjuvant or adjuvant) unless it can unambiguously be determined, e.g. from the partial date, that the medication was started on or after the date of first study medication administration.
- In case day of onset of an adverse event is partially or completely missing it will be assumed that the event is treatment-emergent unless it can be unambiguously determined that this is not the case. In case the relationship code is missing for adverse events, the event will be considered to be related to the study medication.

No other replacement of missing data will be performed.

Imputed data will be flagged in the lists of individual data.

5.5 Repeat/Unscheduled Assessments

The data of repeat/unscheduled assessments for laboratory variables evaluated based upon CTCAE severity grading, for LVEF and for immunogenicity will be considered for the statistical tables. Repeat/unscheduled assessments for the other laboratory variables will be listed only.

For 12-lead ECGs only the scheduled assessments will be considered for the statistical tables.

5.6 Data Listings

Patient data listings will be provided of all tabulated variables, all data used to compute calculated variables and a reference date (date of first dosing) for listings containing dates. Listings will be sorted by study treatment, patient number, visit, and time point. Data listings will include repeat assessments.

5.7 Changes to the Planned Analyses

The protocol uses the term Intention to Treat Population. This was replaced by Full Analysis Set, which is presently more usual. Also, it was decided to consider the mFAS instead of the FAS for the analysis.

The protocol foresaw to perform the final analysis after all patients have completed the post-treatment 2-year follow-up period. On request of regulatory authorities, it was decided to perform an analysis of safety when all patients completed the adjuvant treatment phase, consisting of separate analyses of the neo-adjuvant phase and the adjuvant phase as well as an integrated analysis of both phases. Also, the analysis of adverse events was required to include numbers of events, an analysis by geographical region, further analyses of all adverse events, serious adverse events, adverse events leading to dose modification or discontinuation of study treatment, and adverse events of special interest.

The protocol foresaw to perform the analysis of all efficacy variables for the ITT Population and the PPS, with the PPS the primary analysis set for the primary efficacy variable and the ITT population the primary analysis set for the secondary variables. For consistency with the analysis of the primary efficacy variable, for the secondary efficacy variables determined at the end of the neo-adjuvant treatment period (i.e bpCR and response assessments) the PP population will also be considered as primary analysis set for the analysis.

In order to obtain additional data on patients with sentinel node biopsy procedure and positive nodes at screenings, an additional analysis set was considered, the restricted PPS (rPPS). Supportive analyses of locally assessed tpCR (primary efficacy variable) will be performed on the basis of this set.

The protocol foresaw that a supportive analysis of the locally assessed tpCR (primary efficacy variable) was to be performed considering tpCR assessed by central reading. It was decided by the sponsor to perform the central reading only if deemed required, as judged from the primary analysis of the primary efficacy variable. Furthermore, a tipping point analysis will be applied as a sensitivity analysis of locally assessed tpCR on the mFAS.

The protocol defines Overall response 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 assessments. Upon design of the eCRF it was understood that 'Overall Response' would be a single assessment, globalizing the assessment of response as derived from Mammography, Ultrasound and Clinical assessments. The Steering Committee specified that 3 overall responses should be assessed by patient: a clinically, a Mammography, and an Ultrasound overall response. These three individual responses will be analysed in addition to the

Overall Response reported by the investigator.

The protocol defines EFS and OS as time from Day 1 of therapy until the event/ death. For consistency with regulatory guidance, this has been changed to time from randomisation until the event/death.

The protocol defines EFS as time from Day 1 of therapy until the first observation of disease progression (documented by appropriate imaging techniques) or the date of death due to any cause, in case death occurred within 72 days after the last valid tumour assessment. This definition originates from a draft version of the protocol intended for a metastatic breast cancer population and has not been adapted when switching to a primary breast cancer population. In this SAP it has been updated to make it applicable to a primary breast cancer population.

The protocol foresaw analyses of EFS and OS by means of Kaplan-Meier survival analysis and Cox proportional hazards. It was decided to also perform a second analysis of EFS based on an alternative censoring rule, as well as time to event analyses to investigate the relationship between EFS and locally assessed tpCR and bpCR. In view of the small number of deceases it was decided not to perform the Cox proportional hazards analysis of OS.

In the analysis of the pharmacokinetic data it was initially decided to replace values below lloq with zero for the calculation of the descriptive statistics. Based on feedback from EMA and the request to provide geometric descriptive statistics as well, this decision was updated and values below the lloq were replaced with lloq/2.

Furthermore, while initially the analysis of the PK data took into account all patients of the mFAS, a second analysis was added investigating only patients in the PPS with samples collected within time windows of 19 23 days after administration of the study drug.

5.8 Hypotheses and Decision Rules

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, based on the result of the local reading, is equivalent in the two treatment groups. Equivalence will be concluded if the 95% confidence interval (CI) on the difference of the two proportions is completely contained within the interval [-15.0;+15.0]. As supportive analysis the same analysis is performed based on the central reading results. Furthermore, a concordance analysis was performed comparing local and central reading results.

Secondary efficacy variables considered in the interim analysis are bpCR and response assessed at the time of surgery after neoadjuvant treatment completion after 24 weeks.

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 probability 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 for multiplicity.

6. DETAILS OF THE STATISTICAL ANALYSIS

For all data considered in the analysis patient data lists will be provided. The sections below describe the statistical tables.

6.1 Sample Description

6.1.1 Study Populations

- Date of first and last informed consent and last date of study termination (Total Set).
- Date of first and last administration of neo-adjuvant study drug over all patients (mFAS/SAF).
- Date of first and last surgery or final protocol evaluation/procedure in the neo-adjuvant treatment phase (i.e. EOT visit) (mFAS).
- Date of first and last administration of adjuvant study drug over all patients (aSAF).
- Number of patients in each of the analysis sets, total and broken down by treatment group.

6.1.2 Protocol Deviations

- Frequency distribution of types of protocol deviations (mFAS), total and broken down by treatment group.
- Frequency distribution of types of major protocol deviations (mFAS), total and broken down by treatment group.
- Frequency distribution of types of protocol deviations (PPS), total and broken down by treatment group.

6.1.3 Early Termination

- Frequency distribution of completion of neo-adjuvant treatment period (Yes/No) and if not, of the reasons (SAF).
- Frequency distribution of patients who underwent surgery (Yes/No) and if not, of the reasons (mFAS).
- Frequency distribution of completion of adjuvant treatment period (Yes/No) and if not, of the reasons (SAF).
- Frequency distribution of completion of the post-treatment follow-up period (Yes/No) and if not, of the reasons of discontinuation (PTAS).

6.2 Patient Characteristics

The descriptive analysis of the patient characteristics recorded at onset of the study will be performed for the SAF/mFAS, aSAF, PPS, rPPS and subgroups based on central reading results, for all patients and broken down by treatment group.

6.2.1 Demographic Data

- Descriptive statistics for age.
- Frequency distribution of race.
- Frequency distribution of childbearing potential status.
- Frequency distribution of geographical region.
- Frequency distribution of country.

6.2.2 Breast Cancer History

- Descriptive statistics for time since first diagnosis.
- Frequency distribution of breast(s) concerned.
- Frequency distribution of clinical stage (all categories and regrouped to stratification level) and of histological grade.
- Frequency distributions of differentiation, ploidy, and proliferation.
- Frequency distribution of operable at screening.
- Frequency distribution of oestrogen receptor status.
- For oestrogen-positive patients: descriptive statistics of number of cells.
- Frequency distribution of progesterone receptor status.
- For progesterone-positive patients: descriptive statistics of number of cells.
- Frequency distribution of Oestrogen/Progesterone status
- Frequency distribution of presence of any breast cancer symptom.
- Frequency distribution of presence of each breast cancer symptom.

6.2.3 Imaging Examinations

- Frequency distribution of each type of imaging examination.
- Frequency distribution of combinations of types of imaging examinations.
- Frequency distribution of the result of each type of imaging examination.

6.2.4 Sentinel Node Biopsy

- Frequency distribution of sentinel node biopsy.
- For patients having undergone sentinel node biopsy, frequency distribution of number of nodes taken.
- For patients having undergone sentinel node biopsy, frequency distribution of number of positive nodes.

6.2.5 HER2

- Frequency distribution of HER2 status.
- Frequency distribution of combinations of methods for HER2 determination.
- Frequency distribution of the result for immunohistochemistry (IHC).
- Frequency distribution of the result for FISH/CISH broken down by result for IHC.

6.2.6 Tumour Assessments of the Breast

- Frequency distribution of Mammography performed.
- Frequency distribution of breast largest diameter category as observed with mammography.
- Frequency distribution of Ultrasound performed.
- Frequency distribution of breast largest diameter category as observed with ultrasound.
- Frequency distribution of number of nodes category as observed with ultrasound.
- Frequency distribution of Clinical Tumour Assessment performed.
- Frequency distribution of breast largest diameter category as observed with clinical assessment.
- Frequency distribution of number of nodes category as observed with clinical assessment.

6.2.7 Physical Status and Cardiac Function

- Descriptive statistics of weight at baseline, BMI at baseline, LVEF at screening
- Frequency distribution of ECOG status at baseline, ECG status at screening

6.2.8 Medical and Surgical History

- Frequency distribution of patients with medical/surgical history, total, by MedDRA SOC and by MedDRA SOC and PT.

6.3 Efficacy Data

The efficacy analyses will be performed for the PPS and mFAS. The primary set for the analysis is the PPS.

Supportive analyses of locally and centrally assessed tpCR and bpCR will be performed on the basis of other populations and subsets (see section 6.3.4).

6.3.1 Locally and centrally assessed tpCR

- Frequency distribution and exact 95% Clopper-Pearson CI in each treatment group.
- Frequency distribution and exact 95% Clopper-Pearson CI in each treatment group, broken down for each stratification factor.
- Difference of tpCR in the 2 treatment groups and exact 95% Santner-Snell CI.
- Fisher Exact test comparing the 2 treatment groups.
- Ratio of tpCR in the 2 treatment groups and 95% CI based on normal approximation.
- Logistic regression model comparing the 2 treatment groups adjusting for region, stage, and E2/P4 receptor status: Adjusted difference and ratio of tpCR and corresponding 95% CI and the p-value for the effect of treatment based on the NLMIXED and the GENMOD approach (section 5.2).
- Analysis of the concordance between locally and centrally assessed tpCR.
    - Overall percent agreement based on the proportion of concordant results and exact 95% Clopper-Pearson CI, for all patients and in each treatment group.
    - Positive and negative percent agreement based on frequency distribution and exact 95% Clopper-Pearson CI of local assessment broken down by central assessment, for all patients and in each treatment group.
    - Positive and negative predicted values based on frequency distribution and exact 95% Clopper-Pearson CI of central assessment broken down by local assessment, for all patients and in each treatment group.
    - McNemar test to compare the frequency of central assessment and local assessment, for all patients and in each treatment group.
- A tipping point analysis will be applied as a sensitivity analysis of locally assessed tpCR on the mFAS:
  Within the set of patients with missing locally assessed tpCR, for each combination of proportions with tpCR = 'Yes' in the two treatment groups, the equivalence will be assessed and as such it will be possible to get a full picture of the robustness of the results and the possible influence of different assumptions. The equivalence of the proportions will be assessed in a similar way as for the primary analysis, based on the 95% CI, and without taking into account stratification factors. Similar to the decision in section 3.2.3, patients who did not undergo surgery due to lack of efficacy (i.e. had progressive disease at the end of the neo-adjuvant treatment period or before surgery) will be considered to be non-responders.

6.3.2 Locally and centrally assessed bpCR

- Frequency distribution and exact 95% Clopper-Pearson CI in each treatment group.
- Frequency distribution and exact 95% Clopper-Pearson CI in each treatment group, broken down for each stratification factor.
- Difference of bpCR in the 2 treatment groups and exact 95% Santner-Snell CI.
- Fisher Exact test comparing the 2 treatment groups.
- Ratio of bpCR in the 2 treatment groups and 95% CI based on normal approximation.

- Logistic regression model comparing the 2 treatment groups adjusting for region, stage, and E2/P4 receptor status: Adjusted difference and ratio of bpCR and corresponding 95% CI and the p-value for the effect of treatment based on the NLMIXED and the GENMOD approach (section 5.2)
- Analysis of the concordance between locally and centrally assessed bpCR.
    - Overall percent agreement based on the proportion of concordant results and exact 95% Clopper-Pearson CI, for all patients and in each treatment group.
    - Positive and negative percent agreement based on frequency distribution and exact 95% Clopper-Pearson CI of local assessment broken down by central assessment, for all patients and in each treatment group.
    - Positive and negative predicted values based on frequency distribution and exact 95% Clopper-Pearson CI of central assessment broken down by local assessment, for all patients and in each treatment group.
    - McNemar test to compare the frequency of central assessment and local assessment, for all patients and in each treatment group.

6.3.3 Response at the End of the Neo-Adjuvant Treatment Period

Overall and separately for mammography, ultrasound, and clinical tumour assessment at the end of the neo-adjuvant treatment period (assessed before surgery):

- Frequency distribution of CR/PR/SD/PD/NE in each treatment group.
- Frequency distribution of best overall response and exact 95% Clopper-Pearson CI in each treatment group.
- Frequency distribution of best overall response and exact 95% Clopper-Pearson CI in each treatment group, broken down for each stratification factor.
- Difference of best overall response in the 2 treatment groups and exact 95% Santner-Snell CI.
- Fisher Exact test comparing best overall response in the 2 treatment groups.
- Logistic regression model comparing the 2 treatment groups adjusting for region, stage, and E2/P4 receptor status: Adjusted difference and ratio of the response and corresponding 95% CI and the p-value for the effect of treatment based on the NLMIXED and the GENMOD approach (section 5.2)

NOTE: The above-mentioned analysis was not performed at the end of the Adjuvant period.

6.3.4 Supportive Analysis

<u>For the PPS excluding the Italian sites</u>

- tpCR and bpCR both locally and centrally assessed
    - Frequency distribution and exact 95% Clopper-Pearson CI in each treatment group.
    - Frequency distribution and exact 95% Clopper-Pearson CI in each treatment group, broken down for each stratification factor.
    - Difference of bpCR in the 2 treatment groups and exact 95% Santner-Snell CI.
    - Fisher Exact test comparing the 2 treatment groups.
    - Ratio of bpCR in the 2 treatment groups and 95% CI based on normal approximation.
    - Logistic regression model comparing the 2 treatment groups adjusting for region, stage, and E2/P4 receptor status: Adjusted difference and ratio of bpCR and corresponding 95% CI and the p-value for the effect of treatment based on the NLMIXED and the GENMOD approach (section 5.2)
    - Analysis of the concordance between locally and centrally assessed bpCR.

  - Overall percent agreement based on the proportion of concordant results and exact 95% Clopper-Pearson CI, for all patients and in each treatment group.
  - Positive and negative percent agreement based on frequency distribution and exact 95% Clopper-Pearson CI of local assessment broken down by central assessment, for all patients and in each treatment group.
  - Positive and negative predicted values based on frequency distribution and exact 95% Clopper-Pearson CI of central assessment broken down by local assessment, for all patients and in each treatment group.
  - McNemar test to compare the frequency of central assessment and local assessment, for all patients and in each treatment group.

- Overall response and separately for mammography, ultrasound, and clinical tumour assessment at the before surgery assessment
  - Frequency distribution of CR/PR/SD/PD/NE in each treatment group.
  - Frequency distribution of response and exact 95% Clopper-Pearson CI in each treatment group.
  - Frequency distribution of response and exact 95% Clopper-Pearson CI in each treatment group, broken down for each stratification factor.
  - Difference of response in the 2 treatment groups and exact 95% Santner-Snell CI.
  - Fisher Exact test comparing response in the 2 treatment groups.
  - Ratio of response in the 2 treatment groups and 95% CI based on normal approximation.
  - Logistic regression model comparing the 2 treatment groups adjusting for region, stage, and E2/P4 receptor status: Adjusted difference and ratio of bpCR and corresponding 95% CI and the p-value for the effect of treatment based on the NLMIXED and the GENMOD approach (section 5.2)

<u>For the rPPS</u>

- tpCR and bpCR both locally and centrally assessed
  - Frequency distribution and exact 95% Clopper-Pearson CI in each treatment group.
  - Frequency distribution and exact 95% Clopper-Pearson CI in each treatment group, broken down for each stratification factor.
  - Difference of bpCR in the 2 treatment groups and exact 95% Santner-Snell CI.
  - Fisher Exact test comparing the 2 treatment groups.
  - Ratio of bpCR in the 2 treatment groups and 95% CI based on normal approximation.
  - Logistic regression model comparing the 2 treatment groups adjusting for region, stage, and E2/P4 receptor status: Adjusted difference and ratio of bpCR and corresponding 95% CI and the p-value for the effect of treatment based on the NLMIXED and the GENMOD approach (section 5.2)
  - Analysis of the concordance between locally and centrally assessed bpCR.
    - Overall percent agreement based on the proportion of concordant results and exact 95% Clopper-Pearson CI, for all patients and in each treatment group.
    - Positive and negative percent agreement based on frequency distribution and exact 95% Clopper-Pearson CI of local assessment broken down by central assessment, for all patients and in each treatment group.
    - Positive and negative predicted values based on frequency distribution and exact 95% Clopper-Pearson CI of central assessment broken down by local assessment, for all patients and in each treatment group.
    - McNemar test to compare the frequency of central assessment and local assessment, for all patients and in each treatment group.

For patients of the PPS without symptoms of inflammatory breast

- Overall response and separately for mammography, ultrasound, and clinical tumour assessment at the before surgery assessment
    - Frequency distribution of CR/PR/SD/PD/NE in each treatment group.
    - Frequency distribution of response and exact 95% Clopper-Pearson CI in each treatment group.
    - Difference of response in the 2 treatment groups and exact 95% Santner-Snell CI.
    - Fisher Exact test comparing response in the 2 treatment groups.
    - Ratio of response in the 2 treatment groups and 95% CI based on normal approximation.

For patients of the PPS, separately for each country with at least 10 patients

- Locally assessed tpCR
    - Frequency distribution and exact 95% Clopper-Pearson CI in each treatment group.
    - Difference of tpCR in the 2 treatment groups and exact 95% Santner-Snell CI.
    - Ratio of tpCR in the 2 treatment groups and 95% CI based on normal approximation.
- Locally assessed bpCR
    - Frequency distribution and exact 95% Clopper-Pearson CI in each treatment group.
    - Difference of tpCR in the 2 treatment groups and exact 95% Santner-Snell CI.
    - Ratio of tpCR in the 2 treatment groups and 95% CI based on normal approximation.
- Overall response and separately for mammography, ultrasound, and clinical tumour assessment at the before surgery assessment
    - Frequency distribution of CR/PR/SD/PD/NE in each treatment group.
    - Frequency distribution of response and exact 95% Clopper-Pearson CI in each treatment group.
    - Difference of response in the 2 treatment groups and exact 95% Santner-Snell CI.
    - Ratio of response in the 2 treatment groups and 95% CI based on normal approximation.
- Forest plots ordered by number of patients, based on the ratio between the 2 treatment groups of:
    - Locally assessed tpCR.
    - Locally assessed bpCR.
    - Overall response and separately for mammography, ultrasound, and clinical tumour assessment at the before surgery assessment.

6.3.5 Event-Free Survival

For the primary definition of EFS and the sensitivity analysis:

- Frequency distribution of the occurrence of the first event broken down by treatment group, and by treatment group and each stratification factor.
- Frequency distribution of the type of first event (PD / Local or distant recurrence / Second primary cancer / Death due to any cause), broken down by treatment group.
- Kaplan-Meier Analysis
    - Estimates of Q1, median, and Q3 of EFS time and 95% CIs in each treatment group.
    - Estimate of the EFS rate at 2 years after the end of treatment and 95% CI in each treatment group.
    - Log-rank test to compare the 2 treatment groups.
- Cox proportional hazards regression models
    - Estimate of the EFS hazard ratio and 95% CI between treatment groups, for all patients and for each stratification factor.
    - Evaluation of the treatment effect and the effect of each stratification factor.

The following exploratory analyses of the primary definition of EFS will be performed on the PPS:

- Kaplan-Meier analysis with estimates of the median EFS time, log-rank test, and graphical representation
    - For patients with and without tpCR as locally assessed (the 2 treatment groups together).
    - For patients with and without tpCR as locally assessed, for each treatment group.
- Cox proportional hazards regression with independent variables treatment group, locally assessed tpCR, region, stage, and E2/P4 receptor status
    - Estimate of the EFS hazard ratio and 95% CI between patients with and without locally assessed tpCR.
- Kaplan-Meier analysis with estimates of the median EFS time, log-rank test, and graphical representation
    - For patients with and without bpCR as locally assessed (the 2 treatment groups together).
    - For patients with and without bpCR as locally assessed, for each treatment group.
- Cox proportional hazards regression with independent variables treatment group, locally assessed bpCR, region, stage, and E2/P4 receptor status
    - Estimate of the EFS hazard ratio and 95% CI between patients with and without locally assessed bpCR.

6.3.6 Overall Survival

- Frequency distribution of survival broken down by treatment group, and by treatment group and each stratification factor.
- Kaplan-Meier Analysis
    - Estimates of Q1, median, and Q3 of OS time and 95% CIs in each treatment group.
    - Estimates of the OS rate at 2 years after the end of treatment and 95% CI in each treatment group.
    - Log-rank test to compare the 2 treatment groups.

6.4 Safety Data

The analysis of safety will be descriptive and consist of summary statistics for each treatment group. There will be no statistical tests or models to compare the treatment groups.

The analysis of TEAEs during the neo-adjuvant treatment period and the entire treatment period will be performed on the SAF. The analysis of ATEAEs during the adjuvant treatment period will be performed on the ASAF. The analysis of PTAEs will be performed on the PTAS. The analysis of the other safety data will be performed on the SAF.

6.4.1 Adverse Events

The tables preceded by * will provide frequencies of patients with adverse events as well as the total number of events. The tables preceded by $ will be given for all patients and broken down by geographical region.

The analysis will consist of:

Neo-adjuvant treatment (SAF)

- *$ Frequency distribution and 95% Clopper-Pearson CIs of patients with any:
  - NATEAE
  - NATEAE related to study treatment
  - NATEAE related to chemotherapy
  - NATEAE of Grade 3 or higher
  - Serious NATEAE
  - Serious NATEAE related to study treatment
  - Serious NATEAE related to chemotherapy
  - NATEAE leading to discontinuation of study treatment
  - NATEAE leading to dose modification or discontinuation of study treatment
  - NATEAE related to study treatment leading to dose modification or discontinuation of study treatment
  - Serious NATEAE leading to dose modification or discontinuation of study treatment
  - NATEAE of special interest.
- *$ Frequency distribution of patients with NATEAEs by SOC and by SOC and PT.
- Frequency distribution of patients with NATEAEs by SOC and by SOC and PT, and by maximal severity (grade).
- Frequency distribution of patients with NATEAEs by SOC and by SOC and PT, and by strongest relationship with the study treatment.
- Frequency distribution of patients with NATEAEs by SOC and by SOC and PT, and by strongest relationship with chemotherapy.
- * Frequency distribution of patients with NATEAEs related to study treatment by SOC and by SOC and PT.
- Frequency distribution of patients with NATEAEs related to study treatment by SOC and by SOC and PT, and by maximum severity (grade).
- *$ Frequency distribution of patients with serious NATEAEs by SOC and by SOC and PT.
- * Frequency distribution of patients with NATEAEs leading to dose modification or discontinuation of study treatment by SOC and by SOC and PT.
- * Frequency distribution of patients with NATEAEs related to study treatment and leading to dose modification or discontinuation of study treatment by SOC and by SOC and PT.
- * Frequency distribution of patients with each type of NATEAE of special interest.

Adjuvant treatment (aSAF)

- *$ Frequency distribution and 95% Clopper-Pearson CIs of patients with any:
  - ATEAE
  - ATEAE related to study treatment
  - ATEAE related to chemotherapy
  - ATEAE of Grade 3 or higher
  - Serious ATEAE
  - Serious ATEAE related to study treatment
  - Serious ATEAE related to chemotherapy
  - ATEAE leading to discontinuation of study treatment
  - ATEAE leading to dose modification or discontinuation of study treatment
  - ATEAE related to study treatment leading to dose modification or discontinuation of study treatment
  - Serious ATEAE leading to dose modification or discontinuation of study treatment
  - ATEAE of special interest.
- *$ Frequency distribution of patients with ATEAEs by SOC and by SOC and PT.
- Frequency distribution of patients with ATEAEs by SOC and by SOC and PT, and by maximal severity (grade).
- Frequency distribution of patients with ATEAEs by SOC and by SOC and PT, and by strongest relationship with the study treatment.
- * Frequency distribution of patients with ATEAEs related to the study treatment by SOC and by SOC and PT.
- Frequency distribution of patients with ATEAEs related to the study treatment by SOC and by SOC and PT, and by maximum severity (grade).
- *$ Frequency distribution of patients with serious ATEAEs by SOC and by SOC and PT.
- * Frequency distribution of patients with ATEAEs leading to dose modification or discontinuation of study treatment by SOC and by SOC and PT.
- * Frequency distribution of patients with ATEAEs related to the study treatment and leading to dose modification or discontinuation of study treatment by SOC and by SOC and PT.
- * Frequency distribution of patients with each type of ATEAE of special interest.

Entire treatment period (SAF)

- Same analysis as for adjuvant treatment but based on TEAEs instead of only ATEAEs.
- For each type of TEAE of special interest, separately for all events and for events related to study treatment:
  - * Frequency distribution and 95% CI of patients with events.
  - Total duration of exposure in patient years.
  - Rate per 100 treatment years defined as the total number of events divided by the total duration of exposure.
  - 95% CI on the rate per 100 treatment years based on the exact Poisson CI on the total number of events.
  - Frequency distribution by maximal severity (grade).
  - * Frequency distribution of patients with serious events.
  - Frequency distribution of patients with events by PT. For haematotoxicity the frequency distribution of patients with events is broken down by SMQ and PT.

Post-treatment follow-up period (PTAS)

- *$ Frequency distribution and 95% Clopper-Pearson CIs of patients with any:
  - PTAE
  - PTAE related to study treatment
  - PTAE of Grade 3 or higher
  - Serious PTAE
  - Serious PTAE related to study treatment
- *$ Frequency distribution of patients with PTAEs by SOC and by SOC and PT.
- Frequency distribution of patients with PTAEs by SOC and by SOC and PT, and by maximal severity (grade).
- Frequency distribution of patients with PTAEs by SOC and by SOC and PT, and by strongest relationship with the study treatment.
- * Frequency distribution of patients with PTAEs related to the study treatment by SOC and by SOC and PT.
- Frequency distribution of patients with PTAEs related to the study treatment by SOC and by SOC and PT, and by maximum severity (grade).
- *$ Frequency distribution of patients with serious PTAEs by SOC and by SOC and PT.
- * Frequency distribution of patients with each type of PTAE of special interest.
- For each type of PTAE of special interest, separately for all events and for events related to study treatment:
  - * Frequency distribution and 95% CI of patients with events.
  - Frequency distribution by maximal severity (grade).
  - * Frequency distribution of patients with serious events.
  - Frequency distribution of patients with events by PT. For haematotoxicity the frequency distribution of patients with events is broken down by SMQ and PT.

Patient data lists

- Pre-treatment adverse events
- TEAEs
- Deaths and serious TEAEs
  (Serious pre-treatment events are in the list of pre-treatment events).
- TEAEs Leading to Dose administration modification, Study Treatment Interruption, or Discontinuation
- TEAEs of Special Interest.
- PTAEs.
- Deaths and serious PTAEs.
- PTAEs of Special Interest.
- Adverse events with start date > date of last administration of treatment + 7 months (214 days).

The patient data lists of TEAEs will contain data from both the neo-adjuvant and adjuvant periods.

6.4.2 Laboratory Data

- For each laboratory variable (haematology, chemistry) for which a CTCAE severity grade is determined (see Table 1):
  - Frequency distribution of CTCAE severity grade:
    - At neo-adjuvant baseline.
    - Highest CTCAE severity grade during the neo-adjuvant treatment phase.
    - Highest CTCAE severity grade during the entire treatment period.
    - For patients treated during the adjuvant treatment phase, highest CTCAE severity grade during the adjuvant phase.

    For variables for which there is a bidirectional grade, frequency distributions during the neo-adjuvant and adjuvant treatment phases (after baseline), will be given for low and high values.
  - Shift table of CTCAE severity grade
    - At neo-adjuvant baseline and the highest CTCAE severity grade during the neo-adjuvant treatment phase.
    - At neo-adjuvant baseline and the highest CTCAE severity grade during the adjuvant treatment phase.
    - At neo-adjuvant baseline and the highest CTCAE severity grade during the entire treatment period.

    For variables for which there is a bidirectional grade, separate shift tables will be given for low and high values.
- For the other laboratory variables (hematology, chemistry):
  - Frequency distribution of the status with respect to the normal range at baseline and each scheduled visit after baseline.
  - Shift table between the status with respect to the normal range at baseline and the status with respect to the normal range at each scheduled visit after baseline.

Only patients with post-baseline laboratory values will be included in the shift tables.

6.4.3 Physical Examination and Vital Signs

These data will be listed only

6.4.4 12-Lead ECG

- Frequency distribution of ECG overall interpretation (normal, abnormal not clinically significant, abnormal clinically significant) at each scheduled assessment time.

6.4.5 LVEF

- Descriptive statistics for LVEF at each scheduled visit.
- Descriptive statistics for the change in LVEF between neo-adjuvant baseline and each scheduled visit after neo-adjuvant baseline.
- Frequency distribution of LVEF < 50% any time after neo-adjuvant baseline.
- Frequency distribution of decrease in LVEF from neo-adjuvant baseline > 10% any time after neo-adjuvant baseline.

6.4.6 Immunogenicity

- Frequency distribution of human anti-trastuzumab antibodies status at neo-adjuvant baseline, at each scheduled visit except before Cycle 5, and worst status after baseline.
- Shift table of human anti-trastuzumab antibodies status at baseline and worst status after baseline.
- List of all individual data for patients with any positive ADA result.

6.5 Pharmacokinetic data

The analysis will be performed for mFAS and PPS both based on all samples and on samples taken within 19 – 23 days after study drug administration.

Separately for Cycles 5, 8, 10, and 14, for each patient:

- For each treatment group, descriptive statistics of C_{trough} and additionally the geometric mean and geometric coefficient of variation.
- Ratio of geometric means of C_{trough} of HD201 and Herceptin® and 90% confidence interval (CI).

6.6 Course of the Study

The descriptive analysis will be performed for the SAF (entire study, neo-adjuvant period, chemotherapy, entire treatment period), for the aSAF (adjuvant period), and for the PTAS (post-treatment follow-up period), broken down by treatment group.

6.6.1 Entire Study (SAF)

- Descriptive statistics of study duration.

6.6.2 Post-Treatment Follow-Up Period (PTAS)

- Descriptive statistics of duration of post-treatment follow-up period.

6.6.3 Extent of Exposure

Neo-adjuvant Period (SAF)

- Frequency distribution of the number of cycles study drug was administered.
- Descriptive statistics of cumulative dose administered
- Descriptive statistics of treatment duration.
- Descriptive statistics of dose intensity
- Descriptive statistics of relative dose intensity
- Frequency distribution of relative dose intensity classes
- Frequency distribution of having at least one cycle with dose delay of at least 2 days
- Frequency distribution of having at least one cycle with dose delay due to adverse events of at least 2 days

Adjuvant Period (aSAF)

- Frequency distribution of the number of cycles study drug was administered.
- Descriptive statistics of cumulative dose administered
- Descriptive statistics of treatment duration.
- Descriptive statistics of dose intensity
- Descriptive statistics of relative dose intensity
- Frequency distribution of relative dose intensity classes
- Frequency distribution of having at least one cycle with dose delay of at least 2 days
- Frequency distribution of having at least one cycle with dose delay due to adverse events of at least 2 days

Entire Treatment Period (SAF)

- Frequency distribution of the number of cycles study drug was administered.
- Descriptive statistics of cumulative dose administered
- Descriptive statistics and sum of duration of exposure.
- Frequency distribution of duration of exposure category.
- Descriptive statistics and sum of duration of exposure by duration of exposure category.
- Descriptive statistics and sum of duration of exposure by age category.
- Descriptive statistics and sum of duration of exposure by race.

Chemotherapy (SAF)

Separately for docetaxel, epirubicin, and cyclophosphamide:

- Frequency distribution of number of administrations.
- Frequency distribution of having at least one cycle without full dose administered as per package insert.

For docetaxel, epirubicin, and cyclophosphamide together:

- Frequency distribution of having 8 cycles for which the full dose administered as per package insert and as scheduled in the protocol

6.6.4 Prior and Concomitant Medications and Non-drug Therapy/Surgery

Prior and Concomitant Medications

- Documented list of prior medication (SAF).
- Frequency distribution of patients taking concomitant medication during the neo-adjuvant treatment period by WHO-DRUG anatomical class and by WHO-DRUG anatomical class and therapeutic class (SAF).
- Frequency distribution of patients taking concomitant medication during the adjuvant treatment period by WHO-DRUG anatomical class and by WHO-DRUG anatomical class and therapeutic class (aSAF).

Prior and Concomitant Non-drug Therapy/Surgery

These data will be listed only.

Anti-Cancer Treatment during the Adjuvant Treatment Period

- Frequency distribution of patients taking anti-cancer treatment during the adjuvant treatment period and of patients taking anti-cancer treatment during the adjuvant treatment period by combination of types of treatment (hormonal therapy, radiotherapy) (aSAF).

APPENDIX: Schedule of Assessments

Study procedure	Screening		Neoadjuvant period - Cycle (week) [1]								Before surgery	Adjuvant period[2]	EOT[3]	Follow-up[4]
	-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[5]	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[6]	X		X	X	X	X	X	X	X	X	X	X	X	X
Height and weight[7]	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[8]	X	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG[9]	X						X				X	X	X	X
LVEF (echocardiography or MUGA)[10]	X						X				X	X	X	X
Haematology[11]		X	X	X	X	X	X	X	X	X	X	X	X	

[1] 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.
[2] Adjuvant therapy for 10 cycles.
[3] At 4 weeks after last administration of study medication for patients completing the treatment period of 12 months and those discontinuing from the study.
[4] 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).
[5] Full physical examination at baseline and EOT. During the study, physical examination should be symptom directed.
[6] Vital signs: blood pressure, pulse rate, body temperature.
[7] Body height at screening only
[8] 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.
[9] 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.
[10] 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.
[11] Haematology: haemoglobin, haematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (neutrophils). Laboratory tests must be

Study procedure	Screening		Neoadjuvant period - Cycle (week) [1]								Before surgery	Adjuvant period[2]	EOT[3]	Follow-up[4]
	-28 days	-7 days	1 (w0)	2 (w3)	3 (w6)	4 (w9)	5 (w12)	6 (w15)	7 (w18)	8 (w21)				
Clinical chemistry[1]		X	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity sampling[2]	X										X		X	X
GWAS	X													
Clinical tumour assessment [3]	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 [4]							X			X				
CT/MRI scan, Bone scan [5]	X													
Adverse events [6]	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	

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.**

[1] 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.**

[2] Immunogenicity will be assessed at baseline, before surgery, 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.

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

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

[5] 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.**

[6] 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 stabilized.

AES1_SAP_FIN_1_0

Final Audit Report 2021-08-23

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