# 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.

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| **Ethical review** | Not approved |
| **Status** | Will not start |
| **Health condition type** | Breast neoplasms malignant and unspecified (incl nipple) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON46391

**Source**
ToetsingOnline

**Brief title**
Troika

### Condition

- Breast neoplasms malignant and unspecified (incl nipple)

**Synonym**
operable early breast cancer stage II and III, Patients with HER2-positive

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Archemin
**Source(s) of monetary or material Support:** Prestige Biopharma Pte Ltd

## Intervention

**Keyword:** early breast cancer, Trastuzumab, Troika

## Outcome measures

### Primary outcome

tpCR defined as complete absence of cancer cells in the breast and in the axillary lymph nodes (ypT0/is, ypN0) assessed in specimen obtained during surgery.

### Secondary outcome

Efficacy:

* bpCR defined as complete disappearance of cancer cells in the breast (ypT0/is) at the time of surgery.

* Overall response rate (ORR) defined as proportion of patients whose best overall response is either complete response (CR) or partial response (PR) as assessed by ultrasound and mammography and clinical examination prior to surgery.

* Overall survival (OS) defined as the time from randomisation until death from any cause.

* Event-free survival (EFS) defined as the time from randomisation until progression of disease or death from any cause

Safety and tolerability:

* Safety and tolerability will be assessed using the National Cancer Institute

Common Terminology Criteria for Adverse Events and CTC v4.03

* Cardiac dysfunction will be monitored by 12-lead ECG and measurement of the

LVEF by echocardiography or MUGA scan

* Vital signs

* Clinical laboratory parameters

Immunogenicity:

Incidence of human trastuzumab antibodies at baseline, before surgery, at end

of treatment and one year after completion of trastuzumab therapy.

Pharmacokinetics (and Ctrough):

Sampling will be performed in all patients. At Cycle 5 (Week 12) and Cycle 8

(Week 21), samples will be taken before administration of treatment (Ctrough).

# Study description

**Background summary**

Trastuzumab has become a key component in the care of patients with HER2 positive breast cancer. However, the high costs of Herceptin® therapy is a burden for health care systems and in many countries, patients only have limited access to therapy with biologics due to the high costs of therapy. For these reasons, less expensive alternatives to Herceptin® are sought. This goal may be achieved, at least partly, by the introduction of new biosimilars. Biosimilars are usually cheaper than their reference products and may therefore broaden the access to a drug.
In the TROIKA study, the proposed biosimilar HD201 will be compared to its reference product Herceptin®. The aim of the study is to demonstrate equivalence of HD201 and Herceptin® in terms of efficacy, safety, and pharmacokinetics.

**Study objective**

The primary objective of this study is to show equivalence of the total

pathological complete response rate (tpCR) in patients treated with HD201 plus chemotherapy to that in patients treated with Herceptin® plus chemotherapy. tpCR will be assessed at the time of surgery after neoadjuvant treatment completion after 24 weeks.
Secondary objectives:
*To compare total breast pathological complete response rate (bpCR) between the two arms at the time of surgery.
*To compare overall response rate (ORR) between the two treatment arms at the time of surgery.
*To compare event-free survival (EFS) between the two treatment arms two years after end of treatment.
*To compare overall survival (OS) between the two treatment arms two years after end of treatment.
*To compare immunogenicity of HD201 and Herceptin®.
*To compare safety and tolerability between the two treatment arms.
*To compare the PK trough values of HD201 and Herceptin®.

**Study design**

Randomised, double-blind, parallel group, equivalence, multicentre, international phase III trial.

500 patients with HER2-positive early breast cancer (EBC) will be randomised (1:1) to receive either HD201 in combination with chemotherapy (n=250) or Herceptin® in combination with chemotherapy (n=250).

HD201 or Herceptin® will be administered every 3 weeks for 8 cycles (24 weeks).
Neoadjuvant chemotherapy will be administered as follows:
Cycles 1-4: Docetaxel i.v. 75 mg/m² on day 1 of each cycle.
Cycles 5-8: EC on day 1 of each cycle:
* Epirubicin i.v. 75 mg/m²
* Cyclophosphamide i.v. 500 mg/m²

After administration of the final neoadjuvant study drug dose, surgery will be done within 3-8 weeks followed by an adjuvant treatment period for 10 cycles.

After discontinuation of study medication patients will have an End of Treatment (EOT) visit 4 weeks (± 2 days), after the last administration of study medication, followed by a follow-up period of 2 years.

Sampling for pharmacokinetics (PK) analysis (determination of Ctrough values) will be performed in all patients before cycle 5 and cycle 8.

**Intervention**

Not applicable

**Study burden and risks**

Compared to standard treatment, this study should not lead to any additional burden/inconvenience.

# Contacts

**Public**
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**Scientific**
Archemin

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Able and willing to give written informed consent .
2. Females * 18 years of age.
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) < 2.
4. Known hormone receptor (oestrogen receptor and progesterone receptor) status.
5. HER2 overexpressed as assessed by

o Immunhistochemistry (IHC) or
o Fluorescent in site hybridisation (FISH); FISH positive is defined as FISH amplification ratio * 2.0 / number of HER2 gene copies per cell > 2
o Chromogenic in situ hybridisation (CISH positive)
o Patients with IHC score 3+ or positive FISH/CISH test
o Patients with IHC score 2+ must also have a positive FISH/CISH test.
6. LVEF * 50% or within the normal level of the institution, as assessed by echocardiography or MUGA scan.
7. Life expectancy > 12 weeks.
8. Adequate bone marrow function as evidenced by the following:
o Absolute neutrophils count * 1,500/*L
o Haemoglobin * 9 g/dL
o Platelet count * 100,000/*L
Up to 5% deviation is acceptable.
9. Adequate hepatic and renal function as evidenced by the following:
o Creatinine clearance * 60 mL/min
o Total bilirubin * 1.5 x upper limit of normal (ULN)
o AST (SGOT) and ALT (SGPT) * 2.5 x ULN
Up to 10% deviation is acceptable.
10. Ability to comply with the study protocol.
11. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to first dose of study treatment and agree to use effective contraception (intrauterine device, diaphragm, diaphragm with spermicide or a reliable barrier method, e.g. condom, or condom with spermicide) throughout the study period and 7 months after discontinuation of study drug.
12. Non-metastatic, unilateral, newly diagnosed, operable early breast cancer (EBC) of clinical stage II and III including inflammatory breast cancer.
o Histologically confirmed primary invasive carcinoma of the breast

## Exclusion criteria

1. Metastatic (stage IV) with exception of supraclavicular nodes.
2. Bilateral Breast Cancer
3. Multicentric breast cancer
4. History of any prior invasive breast carcinoma, except for subjects with a history of ductal carcinoma in situ (DCIS) treated with surgery.
5. History of malignant neoplasms within 5 years prior to randomisation, except for curatively treated carcinoma in situ of uterine cervix, basal cell carcinoma of the skin or squamous cell carcinoma of the skin (malignant neoplasms occurring more than 5 years prior to randomisation are permitted if curatively treated with surgery only).
6. Previous history of radiation therapy, anti-neoplastic immunotherapy, chemotherapy or anti-neoplastic biotherapy (including prior HER2 directed therapy).
7. Major surgery within 2 weeks prior to randomisation
8. Serious cardiac illness that would preclude the use of trastuzumab such as:
o history of documented congestive heart failure(CHF) (New York Heart Association, NYHA,

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

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Active |
| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 3 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Herceptin |
| Generic name: | Trastuzumab |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Trastuzumab |
| Generic name: | Trastuzumab |

## Ethics review

Approved WMO

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| Date: | 22-01-2018 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |

Not approved

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|---|---|
| Date: | 08-02-2018 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2016-004019-11-NL |
| ClinicalTrials.gov | NCT03013504 |
| CCMO | NL64434.028.17 |