A multi-centre, open-label, randomized clinical trial comparing the efficacy and safety of the antibody-drug conjugate SYD985 to physician's choice in patients with HER2-positive unresectable locally advanced or metastatic breast cancer

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The primary objective of this study is to demonstrate that SYD985 is superior to physician*s choice in prolonging progression-free survival (PFS) on the basis of the blinded independent central review of tumour assessment.The secondary objectives of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON55876

Source
ToetsingOnline

Brief title
SYD985.002

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer; HER-2 positive locally advanced or metastatic breast tumor

Research involving

Human

Sponsors and support

Primary sponsor: Byondis BV
Source(s) of monetary or material Support: Synthon Biopharmaceuticals BV

Intervention

Keyword: antibody-drug conjugate, Breast Cancer, HER-2 positive, SYD985

Outcome measures

Primary outcome

The primary efficacy endpoint is PFS based on blinded independent central review (ICR) of tumour assessment according to RECIST 1.1. PFS is defined as the time from the date of randomization to the date of first documented ICR-assessed disease progression according to RECIST 1.1 or death due to any cause (whichever occurs earlier).

Secondary outcome

- Overall Survival;

- Objective Response Rate on the basis of the blinded independent central review;

- Investigator assessed PFS;

- Patient reported outcomes for health related quality of life;

Study description

Background summary

Results of the first-in-human Phase I study (SYD985.001) suggest that SYD985 is efficacious and has an acceptable safety profile in heavily pre-treated patients with HER2-positive locally advanced or metastatic breast cancer.

Part I of this Phase I study was a dose escalation study with patients with solid tumors of any origin.
In this part 39 patients were enrolled and treated. For breast cancer patients only (n=25), the objective response rate (ORR) was 36.0% (95% CI 18.0; 57.5), with partial responses in 5 HER2- positive and 4 HER2-negative breast cancer patients. The Kaplan Meier estimate of the median (95% CI) duration of progression free survival (PFS) was 24.3 weeks for the breast cancer patients. All but one HER2-positive breast cancer patients were pretreated with trastuzumab and (ado-)trastuzumab emtansine. Therefore SYD985 represents a reasonable treatment option for the intended patient population in this study.
Part II of the Phase I study is ongoing; expanded patient cohorts with specific cancer types, including late-line HER2-positive locally advanced or metastatic breast cancer, are being evaluated for safety and efficacy.

Study objective

The primary objective of this study is to demonstrate that SYD985 is superior to physician*s choice in prolonging progression-free survival (PFS) on the basis of the blinded independent central review of tumour assessment.

The secondary objectives of this study are to compare the two treatment groups with respect to:
• Overall survival (OS);
• Objective response rate (ORR) on the basis of the blinded independent central review;
• Investigator assessed PFS;
• Patient reported outcomes for health related quality of life;
• Safety and tolerability

Study design

This study is designed as a randomized, active-controlled, superiority study in patients with unresectable locally advanced or metastatic HER2-positive breast cancer. The patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment.
Eligible patients will be randomly assigned (2:1) to receive SYD985 or physician*s choice treatment until disease progression, unacceptable toxicity or study termination by the Sponsor. During treatment, patients will have to visit the clinical site to assess efficacy, quality of life (QoL), and safety using standardized criteria

Intervention

Investigational medicinal product (SYD985 - trastuzumab vc-seco-DUBA):

Patients in the investigational group will be treated every three weeks (Q3W) with 1.2 mg/kg SYD985. SYD985 is an antibody-drug conjugate (ADC) comprised of Synthon's HER2-targeting monoclonal IgG1 antibody trastuzumab (SYD977) covalently bound to a linker-drug (SYD980). The linker-drug contains a cleavable linker and the prodrug seco-duocarmycin-hydroxybenzamide-azaindole (seco-DUBA, SYD978). The linker can be cleaved by proteases in the tumour at the dipeptide valine-citrulline (vc) motif, which releases the active DNA-alkylating toxin (DUBA, SYD986).
Drug product vials contain 80 mg sterile lyophilized SYD985 which should be reconstituted prior to use with 8.0 mL sterile water for injection to yield a solution of 10 mg/mL. SYD985 drug product vials should be stored at 2 to 8 °C (36-46 °F) until use. The calculated amount of solution should be added to an infusion bag containing 100 mL of 0.9% sodium chloride without other additives. If reconstituted vials or the prepared infusion bag is not used immediately, it can be stored at 2 to 8 °C (36-46 °F) for a maximum of 24 hours up to start of infusion. SYD985 is to be administered intravenously over 60 minutes for the first infusion, subsequent infusions can be given over 30 minutes.

Reference therapy: Treatment of physician*s choice:
Patients in the reference group will be treated with approved systemic therapy administered as per local practice and according to the needs of each patient. Investigators can choose between four pre-specified treatment regimens.
• Option 1: Lapatinib + Capecitabine
• Option 2: Trastuzumab + Capecitabine
• Option 3: Trastuzumab + Vinorelbine
• Option 4: Trastuzumab + Eribulin

Study burden and risks

Patients are asked to undergo procedures described in the tables on pages 7 - 9 of the study protocol. These procedures include physical and ophthalmological examination, vital signs (blood pressure, heart rate, body temperature and oxygen saturation), height/weight measurement, urine pregnancy tests (female; childbearing patients) ECG, LEVF, CT or MRI of brain (per clinical indication), whole body bone scan (per clinical indication), tumor assessment, blood draw, ECOF performance status, complete questionnaires and or answer questions of investigator or study team administration of study drug. Additionally, fertile patients who are sexually active must consent to use an effective form of contraception with their sexual partners throughout participation in the study. Patients are also asked to inform their study doctor on their medication use and change in health status.
Adverse drug reactions: Possible adverse drug reactions are described in the Investigator's Brochure. These side effects include nausea, flushing, shivering fits, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of your face or tongue, or trouble swallowing during the infusion or after the infusion on the first day of treatment. All possible adverse drug reactions are described in the Investigator's Brochure. Adverse events while on

physician*s choice treatment are described in the Summary of Product Characteristics and/or Package Insert of the respective treatments.
Risks related to study procedures:
• Blood sampling may cause bruising, fainting, and in rare cases infection.
• During computerized tomography scans (CT-scan) a minimal amount of radiation is used which has no evident risks. The use of a contrast fluid given may lead to itching, rash, hives or feeling warmth throughout the body. These are usually self-limiting reactions that go away rather quickly. In rare cases a more severe allergic reaction may occur.
• Echocardiogram will be done using ECHO or MUGA. There are no known risks from an echocardiogram. The high-frequency sound waves used have not been shown to have any harmful effects. For MUGA scans, allergic reactions to the radioactive tracer are rare, but could occur. Most of the tracer will be eliminated from the body within a day. The amount of exposure is small, and is equal to the amount of radiation that the average person would be exposed to from the environment in a period of 10 days. Occasionally, some soreness or swelling may develop at the injection site.
• The MRI uses a magnetic field and radio waves.
• The slit lamp exam, and the electrocardiogram of the heart are standard examinations and are not associated with any evident risks.
Results of the first-in-human Phase I study (SYD985.001) suggest that SYD985 is efficacious and has an acceptable safety profile in heavily pre-treated patients with HER2-positive locally advanced or metastatic breast cancer.

Contacts

Public
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Scientific
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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. Female patients, age = 18 years old at the time of signing informed consent;
2. Patients with histologically-confirmed, unresectable locally advanced or metastatic breast cancer;
3. Patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment for locally advanced or metastatic disease;
4. HER2-positive tumour status according to the ASCO-CAP guidelines (defined as a 3+ score on immunohistochemistry (IHC) and/or positive by in situ hybridization (ISH)) confirmed by the central laboratory;
5. Patients must have measurable or non-measurable disease that is evaluable per Response Evaluation Criteria for Solid Tumours (RECIST version 1.1). Patients with bone-only sclerotic disease without a lytic component are not eligible;
6. Eastern Cooperative Oncology Group (ECOG) performance status = 2;
7. Estimated life expectancy > 12 weeks at randomization;
8. Adequate organ function, evidenced by the following (local) laboratory results:
- Absolute neutrophil count = 1.5 x 109 /L;
- Platelet count = 100 x 109 /L;
- Hemoglobin = 9.0 g/dL;
- Total bilirubin = 1.5 x the upper limit of normal (ULN);
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) = 3.0x ULN (or = 5.0x ULN in the presence of liver metastases);
- Serum creatinine = 1.5 x ULN;
9. For women of childbearing potential, two methods of effective contraception must be used during the study and up to 6 months after last study treatment. This is not required in case the patient or sole partner is surgically sterilized or in case the patient truly abstains from sexual activity.

Exclusion criteria

1. Having been treated with:
a. SYD985 at any time;
b. Anthracycline treatment within 12 weeks prior to randomization;
c. Other anticancer therapy including chemotherapy, immunotherapy, or investigational agents within 4 weeks prior to randomization;
d. Radiotherapy within 2 weeks prior to randomization;
e. Hormone therapy within 1 week prior to randomization; The patient must have sufficiently recovered from any treatment-related toxicities to NCI CTCAE Grade =1 (except for toxicities not considered a safety risk for the patient at the investigator*s discretion);
2. History of infusion-related reactions and/or hypersensitivity to trastuzumab, (ado-)trastuzumab emtansine or excipients of the study drug which led to permanent discontinuation of the treatment;
3. History of keratitis;
4. Severe, uncontrolled systemic disease (e.g. clinically significant cardiovascular, pulmonary, or metabolic disease) at screening;
5. Left ventricular ejection fraction (LVEF) < 50% as assessed by either echocardiography or multigated acquisition (MUGA) scan at screening, or a history of clinically significant decrease in LVEF during previous treatment with trastuzumab or (ado-)trastuzumab emtansine leading to permanent discontinuation of treatment;
6. Cardiac troponin value above the ULN (local laboratory) at screening;
7. History (within 6 months prior to randomization) of clinically significant cardiovascular disease such as unstable angina, congestive heart failure (CHF), myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication;
8. Untreated brain metastases, symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, or treatment for brain metastases within 8 weeks prior to randomization. Patients with prior treatment of brain metastases must have evidence of disease stability on baseline brain imaging as compared to historical brain imaging;
9. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
10. Known active Hepatitis B or C infection;
11. Major surgery within 4 weeks prior to randomization;
12. Pregnancy or lactation;
13. Other condition, which in the opinion of the investigator, would compromise the safety of the patient or the patient's ability to complete the study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-09-2018
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Trastuzumab vc-seco-DUBA
Generic name:	Not available

Ethics review

Approved WMO Date:	16-08-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	14-02-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-01-2019

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-01-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-03-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2017-001994-18-NL
CCMO	NL62722.100.17