A single-arm phase II trial to evaluate the safety and efficacy of the antibody-drug conjugate SYD985 in patients with HER2-expressing recurrent, advanced or metastatic endometrial carcinoma who previously progressed on or after first line platinum-based chemotherapy

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Clinical Trial Protocol SYD985.003

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1. Protocol synopsis

Title of study A single-arm phase II trial to evaluate the safety and efficacy of the antibody-drug conjugate SYD985 in patients with HER2-expressing recurrent, advanced or metastatic endometrial carcinoma who previously progressed on or after first line platinum-based chemotherapy
Objectives The primary objective of this study is: • To evaluate the objective tumour response rate (ORR) of SYD985; The secondary objectives of this study are to evaluate for SYD985: • Progression-free survival (PFS); • Overall survival (OS); • Safety.
Study design This is an open-label, single-arm study in patients with Human Epidermal growth factor Receptor 2 (HER2)-expressing recurrent, advanced or metastatic endometrial carcinoma. HER2-expression is defined as a 1+, 2+ or 3+ score on immunohistochemistry (IHC) or positive by in situ hybridization (ISH). Inclusion of patients with HER2 1+/2+, ISH negative tumours will be limited to a maximum of 50% of the total sample size. Eligible patients for this study should have progressed on or after first line platinum-based chemotherapy. Patients who have had two or more lines of chemotherapy for advanced/metastatic disease are not eligible. Eligible patients will receive SYD985 every three weeks (Q3W) until disease progression (PD) or unacceptable toxicity. During the first treatment cycle, patients will have to visit the clinical site weekly for safety assessments, followed by one visit in subsequent cycles. Patients who have stopped study treatment for other reasons than PD (e.g. due to toxicity) will continue their tumour evaluations in an observation period until disease progression or start of a new anticancer therapy.
Duration of patient treatment and participation: After a screening period of maximally 28 days, patients who are eligible will be treated until disease progression or unacceptable toxicity. A safety follow-up visit is planned 30 days after the treatment discontinuation visit after which patients may move into an observation period and/or survival follow-up.
Study population The study population will consist of patients complying with the following in- and exclusion criteria:

Inclusion criteria

1. Female patients, age ≥18 years at the time of signing main informed consent;
2. Patients with histologically confirmed recurrent, advanced or metastatic endometrial carcinoma (including endometrioid, mucinous, serous, squamous, clear-cell, undifferentiated or mixed carcinoma or carcinosarcoma);
3. Eligible patients should have progressed on or after one prior systemic platinum-based chemotherapy regimen for endometrial cancer. Patients who have had two or more lines of chemotherapy are not eligible.
   Note:
   – Patients may have received up to one additional line of chemotherapy if given in the neoadjuvant or adjuvant setting provided that such treatment was completed more than 6 months prior to the current tumour recurrence or progression;
   – No more than one line of non-cytotoxic systemic cancer therapy (such as immunotherapy, trastuzumab or protein kinase inhibitors) is allowed;
   Note: there is no restriction regarding to the lines of prior hormonal therapy.
4. HER2 tumour expression defined as a 1+, 2+ or 3+ score on IHC or positive by ISH as determined by the central laboratory on most recent available/obtained tumour material;
5. At least one measurable cancer lesion as defined by the Response Evaluation Criteria for Solid Tumours (RECIST version 1.1);
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;
7. Adequate organ function, evidenced by the following (local) laboratory results:
   – Absolute neutrophil count ≥ 1.5 x 10^9/L;
   – Platelet count ≥ 100 x 10^9/L;
   – Hemoglobin ≥ 9.0 g/dL or 5.6 mmol/L;
   – Total bilirubin ≤ 1.5 x the upper limit of normal (ULN);
   – Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN (or ≤ 5.0 x ULN in the presence of liver metastases);
   – Serum creatinine ≤ 1.5 x ULN;
8. For women of childbearing potential highly effective contraception must be used during the study and up to at least 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. Any HER2-targeting antibody-drug conjugate (ADC) therapy;
   b. Anthracycline treatment within 8 weeks prior to start IMP treatment;
   c. Other anticancer therapy including chemotherapy, immunotherapy, or investigational agents within 4 weeks prior to start IMP treatment or 5 times the half-life of the therapy, whichever is shorter;
   d. Radiotherapy within 4 weeks prior to start IMP treatment, or within 1 week prior to start IMP treatment for palliative care (as long as the lungs were not exposed);
   e. Hormone therapy within 1 week prior to start IMP treatment;
   The patient must have sufficiently recovered from any treatment-related toxicities to 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 or excipients of the study drug which led to permanent discontinuation of the treatment;
3. History or presence 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 leading to permanent discontinuation of treatment;
6. History (within 6 months prior to start IMP treatment) or presence of clinically significant cardiovascular disease such as unstable angina, congestive heart failure (CHF), myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication;
7. Symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, or treatment for brain metastases within 8 weeks prior to start IMP treatment;
8. History or presence of idiopathic pulmonary fibrosis, organizing pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan;
9. Known active Hepatitis B, C or E infection;
10. Major surgery within 4 weeks prior to start IMP treatment;
11. Pregnancy or lactation;
12. 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 medication, mode of administration:

SYD985, *[vic-]trastuzumab duocarmazine*, *Byondis BV, The Netherlands*

SYD985 is an ADC comprised of Byondis' HER2-targeting monoclonal IgG1 antibody trastuzumab covalently bound to a linker-drug. The linker-drug contains a cleavable linker and the prodrug *seco*-duocarmycin-hydroxybenzamide-azaindole (*seco*-DUBA). 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).
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. The calculated amount of solution should be added to an infusion bag containing 0.9% sodium chloride without other additives. SYD985 is to be administered intravenously over 60 minutes for the first infusion, subsequent infusions can be given over 30 minutes.

Study assessments and procedures (see also flowchart)
The informed consent form (ICF) must be signed before any study-related procedure is performed. The pre-screening HER2 testing-ICF should be used to allow the central analysis of HER2 expression on most recent available tumour material from a potentially eligible patient. A fresh tumour biopsy should be performed if no adequate tumour tissue is available. In case the HER2 tumour expression does not comply with the inclusion criterion, the patient cannot participate. Before continuing with full screening the Main-ICF should be signed.

Safety assessments will include physical examination, ECOG performance status, vital signs, weight assessment, electrocardiography (ECG), LVEF measurements by echocardiography or MUGA scan, laboratory measurements, pulmonary function testing (PFT), ophthalmological examination and adverse event (AE) reporting. Blood samples for blood chemistry and haematology will be measured

by the local laboratory. In addition, genetic analysis will be performed by a central laboratory on most recent available tumour tissue and a blood sample, to explore the correlation between biomarkers and tumour response and/or toxicity. The patient will be requested to sign the Genetic tumour analysis-ICF for this purpose.

Patients will be clinically and radiologically (CT or MRI scan) evaluated for tumour response at screening and subsequently during treatment every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Tumour responses will be assessed locally by the investigator/radiologist using RECIST (version 1.1). In addition, scans will be collected and stored at a central imaging lab, for potential central analysis at a later stage. Patients who have stopped study treatment for other reasons than PD (e.g. due to toxicity) will continue their tumour evaluations in an observation period until disease progression or start of a new anticancer therapy.

After a treatment discontinuation visit patients will be contacted to follow up on clinical disease progression, unresolved AEs and new anticancer therapies. After the last study related visit (either 30-day follow up or observation period) patients will be contacted every 3 months to collect overall survival data.

Number of patients and study sites

Approximately 60 patients will be recruited in up to 35-40 participating clinical sites located in Europe, USA and Asia-Pacific. Inclusion of patients with HER2 1+/2+, ISH negative tumours will be limited to a maximum of 50% of the total sample size. This study is of explorative nature; 60 patients should provide for sufficient safety information and for an ORR estimate with acceptable confidence interval for future decision-making.

Estimated clinical study period

First patient First Visit: Q2 2020
Last Patient First Visit: Q3 2021
Study completion for primary endpoint: Q2 2022

1.1. Study flowchart – assessments and procedures

	Screening	Treatment Phase				Treatment discontinuation[16]	Follow-up [17]	Observation phase[18]	Survival Follow up[20]
		Cycle 1[2]			Cycle 2 onwards				
Visit day	**Day -28 to -1**	**Day 1[3]**	**Day 8**	**Day 15**	**Day 1[3]**		**30 days after treatment discont. visit**	**To coincide with tumour evaluation schedule**	**Every 3 months after last contact**
Visit window (days)			**± 1**	**± 1**	**± 3**		**± 7**		**± 14**
Informed consent[1]	✓								
Demographics	✓								
Medical history	✓								
In/exclusion criteria	✓	✓							
Physical examination	✓	✓			✓	✓			
Vital signs[4]	✓	✓	✓	✓	✓	✓			
Weight, height (only at screening)	✓	✓[5]			✓[5]	✓			
ECOG performance status	✓	✓			✓	✓			
PFTs[6]	✓	When clinically indicated							
HER2 assessment[7]	✓								
Genetic tumour analysis[8] including blood sample					Cycle 2				
Haematology / blood chemistry	✓	✓[9]	✓	✓	✓[9]	✓			
Pregnancy test[10]	✓	✓			✓	✓			
LVEF[11,12]	✓				✓ + every 4th cycle	✓			
ECG[13]	✓	✓			✓ + every 4th cycle	✓			
Ophthalmological examination[11]	✓				✓ + every 2nd cycle	✓			
Tumour evaluation[14]	✓	Every 6 weeks for first 24 wks, thereafter every 12 wks				✓		✓[19]	
Study drug administration[15]		✓			✓				
(S)AEs	✓	✓	✓	✓	✓	✓	✓		
Previous and concomitant medication	✓	✓	✓	✓	✓	✓	✓		
Survival information								✓	✓

General note: in case assessments show abnormal results that warrant more extensive monitoring for safety, additional visits and assessments should be considered.

1 Following signing the main study ICF an eligible patient should be treated within 28 days. In addition to the main ICF separate informed consent forms are available for determination of the HER2 tumour status and for genetic tumour analysis;
2 A cycle is defined as 21 days (3 weeks);
3 Day 1 assessments are to be done prior to study drug administration unless otherwise stated;
4 Vital signs should include assessment of blood pressure, heart rate, body temperature and oxygen saturation by pulse oximetry;
5 Weight should always be measured prior to SYD985 administration on the Day 1 visits. However, weight measured up to 7 days before the Day 1 visit can be used for the preparation of the infusion bag;
6 Pulmonary Function Testing (PFTs) should be done at baseline and whenever clinically indicated, according to local hospital standard;
7 Archived tumour material should be submitted for central analysis of HER2 status by IHC and ISH. HER2 status should be available before start IMP treatment. If there is no archival tumour material available a biopsy should be performed to obtain tumour material;
8 Genetic tumour analysis will be performed by a central laboratory. Most recent available tumour tissue should be sent to the central lab together with a blood sample taken on the Cycle 2 Day 1 visit to determine the germline DNA;

9 Blood sampling for haematology/chemistry should be done as closely as possible to the start of the new cycle, but may be done up to 3 days before. Results from the local laboratory should be available before the start of the new cycle to determine if the patient can continue or not. If the screening assessment is done within 5 days before the first study drug administration, analysis does not need to be repeated at the day of first administration;
10 Pregnancy tests (serum test at screening and serum or urinary tests during treatment and at treatment discontinuation) will be performed to exclude pregnancy in women with childbearing potential, and may be done up to 3 days before the start of the new cycle. If the screening assessment is done within 5 days before the first study drug administration, analysis does not need to be repeated at the day of first administration;
11 LVEF assessment as well as ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) should be done as closely as possible to the start of the indicated cycle, but may be done up to 7 days before. Results should be available before the start of the indicated cycle to determine whether the patient can continue;
12 LVEF should be measured by echocardiogram or MUGA scan according to routine local clinical practice, however the method should remain the same per patient. If LVEF is below 50% the next assessment should be performed before the start of the next cycle as indicated in the dose modification Section 9.6.1.3 of the protocol; Assessments should be done at cycle 2 and every 4th cycle, meaning cycle 2, 6, 10 etc.
13 12-lead ECGs should be recorded in triplicate; Assessments should be done at cycle 1 and 2 and every 4th cycle, meaning cycle 1, 2, 6, 10 etc.
14 Tumour evaluation includes systemic use of clinical, radiological (e.g. CT or MRI) and other methods (if deemed necessary). For tumour measurements, a CT or MRI scan should be performed every 6 weeks (± 3 days) for the first 24 weeks and every 12 weeks (± 7 days) thereafter, independent of dosing delays. If tumour evaluation falls at the Day 1 of a cycle (in case there are no treatment delays), it can also be performed up to 7 days prior to the Day 1 visit, but should always be done prior to IMP infusion. The methodology and imaging levels should remain the same at baseline and subsequent evaluations for a given patient. Additionally, scans should be provided to the central imaging lab for collection and storage;
15 Administration of SYD985 in a 21-days regimen (± 3 days) until disease progression or unacceptable toxicity. No recalculation of the SYD985 dose in mg is needed if the weight at the day of administration has changed < 5% compared to the weight at Cycle 1 Day 1. Concomitant prophylactic lubricating eye drops should be prescribed to patients, to be used 3 times a day or as needed;
16 The treatment discontinuation visit should occur at the time study treatment is discontinued for any reason. Tumour evaluation at the discontinuation visit is required for patients who discontinue study treatment before first scheduled in-treatment tumour assessment (week 6) and for patients whose previous tumour assessment did not demonstrate PD and was done more than 21 days prior to the treatment discontinuation period. For patients who continue into the Observation Phase there is no need to perform a tumour evaluation at the discontinuation visit, they should maintain the same tumour evaluation schedule as during the Treatment Phase;
17 If a follow-up visit is not possible, the patient should be contacted by telephone;
18 The Observation Phase is for any patient that discontinued study treatment for reasons other than PD (e.g. toxicity). Patients stay in the Observation Phase until the time of PD or the start of a new anticancer treatment;
19 Tumour imaging for the Observation Visits should be maintained by the same schedule that was initiated during the Treatment Phase;
20 Every 3 months (±14 days) following the last visit/contact (i.e. 30-day follow up visit or final observation phase visit) patient should be contacted for survival until death, lost to follow-up or consent withdrawal, whichever comes first. During this follow-up only survival information and initiation of new anticancer medication should be documented.

2. Sponsor information and responsibilities

A current version of all contact information for functions involved in the clinical study conduct and emergency contacts will be maintained in the Trial Master File (TMF) and Investigator Site File (ISF). The protocol will therefore not be amended for changes in e.g. responsibilities, contact information details as presented below.

Sponsor:	**Byondis BV** Microweg 22 6545 CM Nijmegen The Netherlands
Clinical Project Leader Telephone number: E-Mail:	[redacted]
CRO (clinical services):	[redacted]
EDC services	[redacted]
IMP logistics:	[redacted]
Central Image Vendor: **(collect and hold scans, potential RECIST evaluation)**	[redacted]
Central laboratory **(for HER2 tumour expression):**	[redacted]

Central laboratory
(for genetic tumour analysis)

[redacted]

3. Table of contents

4. List of abbreviations

ABG	Arterial Blood Gas
ADA	Anti-Drug Antibody
ADC	Antibody-Drug Conjugate
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	ALanine aminoTransferase
AP	Alkaline phosphatase
AST	ASpartate-amino-Transferase
ATC	Anatomical therapeutic chemical classification system
BUN	Blood urea nitrogen
CBR	Clinical Benefit Rate
CHF	Congestive heart failure
CI	Confidence Interval
CK	Creatine kinase
CR	Complete response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DUBA	DUocarmycin hydroxyl Benzamide Azaindole
ECG	Electro Cardio Gram
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
HER2	Human Epidermal growth factor Receptor 2
IB	Investigator's Brochure
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
INN	International Non-proprietary Name
IRB	Institutional review Board
ISF	Investigator Site File
ISH	In situ hybridization
IUD	Intrauterine device
IUS	Intrauterine system
LDH	Lactate DeHydrogenase
LVEF	Left Ventricular Ejection Fraction

MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multigated acquisition
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PFT	Pulmonary Function Test
PR	Partial response
Q3W	Dosing every three weeks
RECIST	Response Evaluation Criteria for Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
SYD985	trastuzumab vc-*seco*-DUBA
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
ULN	Upper limit of normal
vc	Valine-citrulline

5. Introduction

5.1. Therapeutic background and study rationale

Endometrial cancer is the second most common gynaecologic malignancy world-wide, with an estimated 380,000 new cases and 90,000 deaths in 2018.[1] Metastatic disease remains non curable. For advanced, metastatic disease platinum-based chemotherapy is the preferred first treatment line.[2,3] Few chemotherapy agents have been shown to produce meaningful response rates in the second-line setting, highlighting a need for new therapies in advanced, recurrent, metastatic endometrium cancer.[4]

Human Epidermal growth factor Receptor 2 (HER2) provides critical signalling for cancer cell growth, survival, and proliferation.[5,6] Amplification and over-expression of HER2 are associated with shortened survival in breast cancer.[7,8] Four HER2-targeting therapies have been approved up to now in the EU and the US for HER2-positive breast cancer: two antibodies (trastuzumab and pertuzumab), antibody-drug-conjugate (ADC) (ado-trastuzumab emtansine, T-DM1), and a small molecule kinase inhibitor (lapatinib).

According to literature on average 25-30% of patients with endometrial cancer have HER2-positive disease.[9,10,11,12]. In an aggressive endometrial cancer subtype of uterine serous carcinoma the addition of trastuzumab to a chemotherapy combination of carboplatin/paclitaxel has shown increased progression-free survival (PFS) in HER2-positive patients.[13]

Byondis developed a new HER2-targeting therapy, SYD985, which is comprised of Byondis' monoclonal IgG1 antibody trastuzumab covalently bound to a linker-drug. This linker-drug contains a cleavable linker and the prodrug *seco*-DUocarmycin-hydroxyBenzamide-Azaindole (*seco*-DUBA). After binding to HER2 on the cell membrane, SYD985 undergoes receptor mediated internalization and the linker is cleaved in the lysosome at the dipeptide valine-citrulline (vc) motif by proteases. Upon cleavage, two self-elimination reactions occur to generate the prodrug (*seco*-DUBA), which then spontaneously rearranges to form the active toxin (DUBA). The active toxin alkylates DNA resulting in DNA damage in both dividing and non-dividing cells, and ultimately cell death. In addition, *in vitro* studies showed that the active toxin can cross the cell membrane and kill neighbouring, HER2-negative tumour cells as a bystander effect (see for more details the Investigator's Brochure (IB)).

Results of the first-in-human Phase I study suggest that SYD985 is efficacious and has an acceptable safety profile in heavily pre-treated patients with HER2-expressing metastatic cancer.[14] In the HER2-positive breast cancer cohort an objective response was achieved by 16 (33%, 95% CI 20.4-48.4) of 48 patients and a median PFS of 7.6 months (95% CI 4.2-10.9). Further investigation of SYD985 is ongoing in a phase III study comparing the efficacy and safety of SYD985 to physician's choice in patients with HER2-positive unresectable locally advanced or metastatic breast cancer.

In the endometrial cancer cohort of the Phase I study, 13 patients were enrolled and treated with SYD985. The objective response rate (ORR) was 39% (95% CI 13.9-68.4), with partial responses in 5 patients. These partial responses were observed both in patients with high- and low-expressing HER2 tumours. Median PFS was 4.3 months (95% CI: 2.4-9.9).[14]

The intent of this Phase II study is to further investigate the efficacy and safety of SYD985 for the treatment of patients with HER2-expressing recurrent, advanced or metastatic endometrial cancer who have progressed on first line platinum-based chemotherapy.

5.2. Patient population rationale

The patient population for this study includes patients with HER2-expressing recurrent, advanced or metastatic endometrial cancer who have progressed after receiving primary treatment with platinum-based chemotherapy. Patients may have had prior chemotherapy in the neoadjuvant or adjuvant setting.

Few agents have been shown to produce meaningful response rates in the second-line setting and no HER2-targeting therapies have been approved yet for endometrial cancer while 25-30% of the patients overexpress the HER2-receptor.

Patients who have received one previous line of HER2-targeting therapy and who have developed resistance to this therapy are eligible, as clinical data suggests that HER2-positive cancers continue to depend on HER2 at the time of progression.[15,16] In addition, efficacy has been demonstrated in the phase I study with SYD985 in patients with breast cancer after having received multiple prior HER2-targeting therapies.

As it is not known what minimal level of HER2-expression is required to initiate an anti-tumour effect with SYD985 in endometrial cancer, and considering the promising results in the phase I study, both patients with high- and patients with low-expressing HER2 tumours will be included in this study, where the patients with HER2-low tumours will not exceed more than 50% of the total sample size.

5.3. Dosage rationale

SYD985 will be administered in a dose of 1.2 mg/kg once every three weeks.

The 3-weekly interval was investigated in the dose-escalation part of the Phase I study and is the regimen chosen to investigate in the ongoing phase III and in this phase II trial. Dosing delays and reductions are allowed to reduce toxicity in an individual patient (Section 9.6).

5.4. Primary endpoint rationale

The primary endpoint of this study is to evaluate the anticancer activity of SYD985 with respect to ORR.

ORR will be defined as the percentage of patients with a best overall response of complete response (CR) or a partial response (PR). This is an established measure of anti-tumour activity, as tumour reduction is a direct therapeutic effect whereas stable disease (SD) could reflect the natural history of the disease. The objective tumour response will be assessed by the investigators using RECIST 1.1.[17]

5.5. Safety considerations

This section is primarily based on the clinical data from the phase I and ongoing phase III study with SYD985. Please refer to the SYD985 IB for further information. It should be taken into account that toxicity other than described in the IB may evolve. For the most up to date information one should always refer to the current version of the IB.

The most common drug-related AEs reported in the clinical studies (>10%) are:

- Conjunctivitis, dry eye, keratitis, lacrimation increased;
- Fatigue;
- Nausea, stomatitis;
- Alopecia, skin hyperpigmentation;
- Neutropenia, anaemia;
- Decreased appetite;

In addition, specific important safety considerations are described in more detail below.

Ocular toxicity

Ocular toxicity was commonly reported with SYD985. Patients previously reported treatment-related ocular toxicity, including most commonly conjunctivitis, dry eye, keratitis and lacrimation increased. Most eye disorders were of mild or moderate intensity. The most common severe AEs were keratitis and conjunctivitis. In the majority of patients, the ocular toxicity improves and eventually recovers, but it may take several months.

Ocular toxicity should be monitored prior to initiation of treatment and every other cycle by an ophthalmological examination (see Section 1.1). Patients with a history of keratitis are not eligible for this study. Specific guidelines regarding dose delays and/or reductions or discontinuation for severe ocular toxicity are provided in Section 9.6.1.1.

Pulmonary toxicity

Pulmonary events, including Interstitial Lung Disease (ILD)/pneumonitis, dyspnoea (exertional), pleural effusion and respiratory failure, have been reported with SYD985. So far one fatal pneumonitis event has been reported at 2.4 mg/kg in the phase I study and one possibly related case of fatal respiratory failure at 1.2 mg/kg in the phase III study.

Caution should be exercised when a patient presents with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, dyspnoea or radiological features on chest CT scan. To detect pneumonitis or other pulmonary toxicity in an early stage, tumour evaluation CT scans should be carefully evaluated for lung changes e.g. by means of high resolution CT. Infectious and disease-related aetiologies should be ruled out. Patients should be advised to promptly report any new or worsening respiratory symptoms.

The diagnosis of ILD/pneumonitis should be made on clinical/radiological findings. Biomarkers for ILD/pneumonitis are exploratory and they should not be used for diagnosis or monitoring of drug induced ILD/pneumonitis. When evaluating ILD/pneumonitis (regardless of stage) it is highly recommended to include a pulmonary consult, a high resolution CT, pulmonary function testing (PFT), pulse oximetry and arterial blood gases (ABGs).

In case pneumonitis is suspected one should consider treatment with a sufficiently high dose of corticosteroids followed with an adequate taper period as per standard hospital protocol for drug-induced pneumonitis. Specific guidance for dose modifications for pneumonitis is described in Section 9.6.1.2.

Cardiac toxicity
Decreased left ventricular ejection fraction (LVEF) was reported as treatment-related AE in a small number of patients treated with SYD985. The majority of events was reported as recovered. No other significant cardiotoxicity has been reported with SYD985 to date. SYD985 should be delayed or discontinued in cases of left ventricular dysfunction according to the guidance in Section 9.6.1.3.

Infusion related reactions
Infusion related reactions were reported for some patients treated with SYD985. All infusion related reactions occurred at the start of the study drug treatment, either after the first and/or second infusion, and SYD985 treatment was continued in all patients. The most common symptoms included chills/ shivering and fever that mostly recovered within 1 day.

Infusion related reactions mostly occur during or immediately following the (initial) infusion. Infusions should be slowed or interrupted for patients experiencing infusion-related symptoms.

Injection site reactions
Injection site reaction was reported in a few patients. Infusion site extravasation was reported sporadically.

It is recommended to avoid the use of veins over joints or in extremities with compromised venous or lymphatic drainage. At the end of each infusion, the line must be flushed with up to 100 mL of sterile 0.9% sodium chloride for infusion, at the discretion of the investigator. When extravasation is noted, immediately stop the infusion and follow the local hospital extravasation protocols for vesicant drugs in consultation with the responsible physician.

Haematological toxicity
Treatment-related haematotoxicity, with neutropenia and anemia as the only treatment-related haematological events reported for more than 10% of patients, were mostly mild or moderate in intensity and only a few patients discontinued SYD985 treatment due to it (all decreased platelet count). Of the patients that recovered, the majority either did not require any intervention or recovered after delayed dosing. Dose modification for haematological events is described in Section 9.6.1.4.

Embryo-foetal toxicity
There are no data from the use of SYD985 in pregnant women. Although specific studies to assess a potential effect of SYD985 on fertility or embryonic development have not been conducted, it is likely that SYD985 can have an effect on fertility and is a developmental toxin based on the DNA reactive nature of the toxin. Therefore, pregnant and lactating women are not eligible to participate in clinical studies with SYD985. Participating patients must use highly effective methods of contraception as described in Section 10.3. In case a patient becomes pregnant during SYD985 treatment, she must be discontinued from the study.

5.6. Benefit-risk assessment

Currently there are few to none treatment options available beyond first-line chemotherapy for patients with advanced or metastatic endometrial cancer that provide a clinically meaningful benefit.

As described in Section 5.5, in previous studies SYD985 was associated with dose-related ocular and pulmonary toxicities. These toxicities are also commonly observed with other ADCs.[18,19] Frequent safety assessments such as ophthalmological and physical examinations, haematology/biochemistry and ECG/LVEF measurements are included in the study to early detect and adequately monitor toxicities when they occur. Clear instructions for dose modifications, i.e. dose delay, reduction or discontinuation, are provided in Section 9.6 specifically for ocular, lung, cardiac and haematological toxicity. In addition, investigators will be instructed to carefully evaluate the tumour evaluation scans for any lung changes. Patients with a history or presence of keratitis, impaired cardiac function and/or lung disease are excluded from the study as these patients may potentially be at higher risk to develop significant treatment-related toxicity.

Based on the efficacy and safety data observed in the clinical phase I and III study and the implemented safety measures in this study, the benefit-risk assessment supports clinical development of SYD985 in this patient population.

6. Objective(s)

6.1. Efficacy objectives

6.1.1. Primary objectives

The primary objective of this study is to evaluate the ORR of SYD985.

6.1.2. Secondary objectives

The secondary objectives of this study are to evaluate SYD985 with respect to:
- Progression Free Survival (PFS);
- Overall Survival (OS);
- Safety.

6.1.3. Other objectives

The other objectives of this study are as follows:
- To describe time to response;
- To describe duration of response;
- To describe the clinical benefit rate (CBR);
- To explore genomic profile/response relationships.

7. Study design

This is an open-label, single-arm study in patients with HER2-expressing recurrent, advanced or metastatic endometrial carcinoma. This is defined as a 1+, 2+ or 3+ score on immunohistochemistry (IHC) and/or positive by in situ hybridization (ISH). Inclusion of

patients with HER2 1+/2+, ISH negative tumours will be limited to a maximum of 50% of the total sample size. Eligible patients for this study should have progressed on or after first line platinum-based chemotherapy. Patients who have had two or more lines of chemotherapy for advanced/metastatic disease are not eligible.

Eligible patients will receive SYD985 1.2 mg/kg every three weeks (Q3W) until disease progression (PD) or unacceptable toxicity. During the first treatment cycle, patients will have to visit the clinical site three times for safety assessments, followed by one visit in subsequent cycles. Patients who have stopped study treatment for other reasons than PD (e.g. due to toxicity) will continue their tumour evaluations in an observation period until disease progression or start of a new anticancer therapy.

8. Study population

The study population will consist of patients with HER2-expressing recurrent advanced or metastatic endometrial carcinoma. Patients should comply with all inclusion and none of the exclusion criteria as described below. All patients must provide their written informed consent before any protocol specific procedure including screening procedures, are performed.

8.1. Eligibility criteria

8.1.1. Inclusion criteria

Any patient must meet the following inclusion criteria:

1. Female patients, age ≥18 years at the time of signing main informed consent;
2. Patients with histologically confirmed recurrent, advanced or metastatic endometrial carcinoma (including endometrioid, mucinous, serous, squamous, clear-cell, undifferentiated or mixed carcinoma or carcinosarcoma);
3. Eligible patients should have progressed on or after one prior systemic platinum-based chemotherapy regimen for endometrial cancer. Patients who have had two or more lines of chemotherapy disease are not eligible.
   Note:
   - Patients may have received up to one additional line of chemotherapy if given in the neoadjuvant or adjuvant setting provided that such treatment was completed more than 6 months prior to the current tumour recurrence or progression;
   - No more than one line of non-cytotoxic systemic cancer therapy (such as immunotherapy, trastuzumab or protein kinase inhibitors) is allowed;

   Note: there is no restriction regarding to the lines of prior hormonal therapy.
4. HER2 tumour expression defined as a 1+, 2+ or 3+ score on IHC and/or positive by ISH as determined by the central lab on most recent available/obtained tumour material;
5. At least one measurable cancer lesion as defined by the Response Evaluation Criteria for Solid Tumours (RECIST version 1.1);
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;

7. Adequate organ function, evidenced by the following (local) laboratory results:
   - Absolute neutrophil count ≥ 1.5 x 10^9/L;
   - Platelet count ≥ 100 x 10^9/L;
   - Hemoglobin ≥ 9.0 g/dL or 5.6 mmol/L;
   - Total bilirubin ≤ 1.5 x the upper limit of normal (ULN);
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN (or ≤ 5.0 x ULN in the presence of liver metastases);
   - Serum creatinine ≤ 1.5 x ULN;
8. For women of childbearing potential highly effective contraception must be used during the study and up to at least 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;

8.1.2. Exclusion criteria

Any patient who meets any of the exclusion criteria below must be excluded from participation in the study:

1. Having been treated with:
   a. Any HER2-targeting ADC therapy;
   b. Anthracycline treatment within 8 weeks prior to start IMP treatment;
   c. Other anticancer therapy including chemotherapy, immunotherapy, or investigational agents within 4 weeks prior to start IMP treatment or 5 times the half-life of the therapy, whichever is shorter;
   d. Radiotherapy within 4 weeks prior to start IMP treatment, or within 1 week prior to start IMP treatment for palliative care (as long as the lungs were not exposed);
   e. Hormone therapy within 1 week prior to start IMP treatment;

   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 or excipients of the study drug which led to permanent discontinuation of the treatment;
3. History or presence of keratitis;
4. Severe, uncontrolled systemic disease (e.g. clinically significant cardiovascular, pulmonary, or metabolic disease) at screening;
5. 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 leading to permanent discontinuation of treatment;
6. History (within 6 months prior to start IMP treatment) or presence of clinically significant cardiovascular disease such as unstable angina, congestive heart failure (CHF), myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication;
7. Symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, or treatment for brain metastases within 8 weeks prior to start IMP treatment;
8. History or presence 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;
9. Known active Hepatitis B, C or E infection;

10. Major surgery within 4 weeks prior to start IMP treatment;
11. Pregnancy or lactation;
12. 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.

8.2. Screen failures and re-screening

Patients who signed the pre-screening HER2 testing-informed consent form (ICF) and/or the Main-ICF but failed to meet the inclusion and/or exclusion criteria are defined as pre-screen or screen failures.

Re-screening is not allowed, a patient who failed one of the in- or exclusion criteria cannot be screened again at a later time point, except for HER2 tumour expression. In case the HER2 tumour staining was unevaluable, it is allowed to send in new material for re-analysis.

9. Study medication and dosing instructions

9.1. Description of study drug

Investigational medicinal product	
Test Product:	SYD985: trastuzumab vc-*seco*-DUBA INN = [vic-]trastuzumab duocarmazine
Formulation:	Drug product vials contain 80 mg lyophilized SYD985 drug product which should be reconstituted prior to use with 8.0 ml of sterile water for injection to yield a solution of 10 mg/mL.
Excipients:	[redacted]
Manufacturer:	Byondis BV, The Netherlands

9.2. Labeling, packaging and storage

SYD985 will be labelled according to Good Manufacturing Practice Annex 13. The drug labels are designed according to the locally applicable regulations and will generally contain the Sponsor name, protocol number, batch number, expiry date (where required), drug product name and content, route of administration, and storage conditions, as appropriate. Individual infusion bags will be prepared by the hospital pharmacy and will be labelled according to the local procedures.

SYD985 should be stored in a secure, limited access location and kept out of sight and reach of children. The vials should be stored in the refrigerator at 2 to 8 °C (36-46 °F) and should not be frozen. The supplies should not be used beyond the expiry date.

Reconstituted vials and prepared infusion solutions should be used immediately, or can be temporarily stored at 2 to 8 °C (36-46 °F) for use within 24 hours after reconstitution of the vial.

9.3. Treatment assignment

When all screening data are available and patient eligibility has been confirmed by the Contract Research Organization (CRO)/Sponsor, the patient will be assigned SYD985 treatment as long as enrolment is not yet completed. A patient should start study treatment within 28 days of signing the Main-ICF.

Enrolment of patients with a HER2-tumour status of IHC 1+, 2+ and ISH-negative or IHC 3+ and/or ISH-positive will be monitored and stopped when 50% (30 patients) have been enrolled in each sub-group.

9.4. Treatment regimen and individual administration procedure

SYD985 1.2 mg/kg will be administered once every three weeks (± 3 days) by intravenous infusion using an infusion set with filter as specified in the pharmacy manual.

The infusion should be prepared aseptically. Slowly inject 8.0 ml sterile water for injection into the 80 mg SYD985 vial to yield a solution of 10 mg/mL. The vial should be swirled gently until completely dissolved. DO NOT SHAKE. Let the vial stand undisturbed for 5 minutes before further use. Inspect the solution for particulates and discoloration. The solution should be clear to slightly opalescent and free of visible particles. The solution should be colourless to pale yellow. Do not use the solution if it contains visible particles or is cloudy or discoloured. The reconstituted vials should preferably be used immediately but can be stored temporarily (see below).

The volume of the SYD985 solution needed for a particular patient should be calculated based on the weight of the patient. The weight should always be measured prior to IMP infusion at the Day 1 visits. However, weight measured up to 7 days before the Day 1 visit can be used for the preparation of the infusion bag. If the weight at a dosing day differs more than 5% from the Cycle 1 Day 1 measurement the actual weight should be used for the preparation.

The required volume needs to be withdrawn from the vial(s) and added to a 100 ml infusion bag as specified in the pharmacy manual containing 0.9% sodium chloride without other additives. To mix the solutions the infusion bag should be gently inverted to avoid foaming.

In case the reconstituted vial and/or prepared infusion bag is not used immediately, they can be stored at 2 to 8 °C (36-46 °F). The prepared infusion bag must be used within 24 hours after reconstitution of the vial.

The first infusion should be administered over 60 minutes (± 10 minutes). Following the initial dose, patients will be observed for at least 90 minutes after end of infusion for fever, chills, or other infusion-related symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions) subsequent infusions can be given over 30 minutes (minimum of 25 minutes), with a minimum 30-minute observation period following the end of infusion.

For each SYD985 infusion, it is recommended to avoid, if possible, the use of veins over joints or in the extremities with comprised venous or lymphatic drainage. At the end of every infusion, the infusion line must be flushed with sterile 0.9% sodium chloride solution for infusion as

indicated in the pharmacy manual, at the discretion of the investigator. In case extravasation is noted, the infusion should be stopped immediately and the local hospital extravasation protocol for vesicant drugs should be followed.

Infusions may be slowed or interrupted for patients experiencing infusion-related symptoms at the discretion of the investigator. Infusion of SYD985 should be interrupted for patients who develop dyspnoea or clinically significant hypotension, but may resume at decreased infusion rate when sufficiently recovered. Infusions may be restarted at the full rate during the next cycle, provided there is adequate monitoring. Adequate premedication should be considered at the discretion of the investigator. Patients who experience a Grade 4 infusion-related reaction or a Grade 3 infusion-related reaction which does not respond to symptomatic medication and/or temporary interruption of infusion or infusion rate reduction should be discontinued from study treatment.

Prophylactic lubricating eye drops should be prescribed to patients, to be used 3 times a day or as needed. All patients are advised not to wear contact lenses or rub their eyes during SYD985 treatment.

9.5. Treatment compliance and accountability

SYD985 will be administered to the patient by trained staff of the study site. Details of preparation and administration will be documented in the electronic Case Report Form (eCRF).

All Investigation Medicinal Product (IMP) will be tracked and accounted for at the investigational site following receipt, dispensing and administration to the patient, and ultimately including destruction or return to the Sponsor/CRO. In case of missing or damaged medication cartons or vials, this is to be reported to the Sponsor/CRO according to the instructions provided in the Pharmacy Manual. The product accountability will be fully documented by the investigational site. The investigational site will retain all unused study drug (and outer packaging) until the drug accountability has been checked by the clinical research associate (CRA).

9.6. Dose modifications

Patients should be assessed for toxicity prior to each dose: dosing should only occur if the clinical assessment and laboratory test values are acceptable. Dosing delays and reductions are designed to maximize treatment for those who derive clinical benefit from treatment while ensuring patient safety.

Irrespective of the reason, if dosing is delayed, dosing should be resumed within 42 days from the last dose received, or the patient should discontinue treatment. On a case-by-case basis it can be decided to postpone dosing for a longer duration, e.g. in case the patient has clearly benefit from study drug treatment. Please contact the Medical Monitor for approval.

Dose delays for SYD985-related toxicities, other than the ones specified below, should be handled as follows:

- If significant SYD985-related toxicities have not recovered to Grade 1 or baseline, the next scheduled dose may be delayed for up to 42 days from the last dose received. “Significant” and “related” will be based on the judgement of the investigator (in

consultation with the Medical Monitor). For example, alopecia even if considered related would most likely not be considered to be significant. Fatigue may or may not be considered either related or significant.

- In general, when the significant and related toxicity (or any other toxicity that the investigator chooses to delay dosing for) resolves to Grade 1 or baseline or is sufficiently resolved in the opinion of the investigator, the patient may resume SYD985 if the delay has not exceeded 42 days from the last received dose. Patients should be re-evaluated weekly during the delay whenever possible. If dosing resumes, the patient may receive SYD985 either at the same dose level as before or the dose can be reduced, at the discretion of the investigator. The dosing interval for subsequent cycles should remain every 21 days.
- If toxicity does not resolve sufficiently within 42 days from the last dose received, the patient should be discontinued from study treatment and should be followed in the observation period for PD as described in Section 11.18.5.

If a patient needs a dose reduction the dose should be reduced from 1.2 mg/kg to 0.9 mg/kg. Patients on the 0.9 mg/kg dose who develop an AE necessitating further dose reductions should be reduced to 0.6 mg/kg. Patients on the 0.6 mg/kg dose who develop an AE necessitating further dose reductions should be discontinued from treatment. Dose escalation is not allowed after a dose reduction.

Protocol requirements for specific toxicities are outlined below.

9.6.1.1. Dose modifications for ocular toxicity

Patients who experience Grade 3 (or higher) ocular toxicity should be discontinued from treatment. For patients who experience Grade 2 ocular toxicity, it should be considered to delay dosing for up to 42 days from the last received dose and appropriate treatment with eye drops, cream, or gel should be applied (e.g. steroid containing eye drops). If study drug is interrupted for Grade 2 toxicity it should resolve to Grade 1 or baseline before restarting treatment. Patients may continue treatment at the same dose level as before or the dose can be reduced, at the discretion of the investigator. Subsequent dosing delays or treatment discontinuation should be considered in case the ocular toxicity persists. The ocular toxicity should be monitored by an ophthalmologist (or qualified delegate) for recovery.

9.6.1.2. Dose modifications for pulmonary toxicity

Patients who experience ILD/pneumonitis Grade ≥ 2 will be discontinued from treatment. For patients who experience Grade 1 ILD/pneumonitis dosing must be delayed for up to 42 days from the last received dose. When the ILD/pneumonitis resolves to Grade 0 patients may continue treatment and a dose reduction should be considered. Reversibility or stabilisation of ILD/pneumonitis should be monitored and documented. If in addition to SYD985 a patient is receiving co-medication and develops drug-induced ILD/pneumonitis this should be considered related to SYD985.

Caution should be exercised when a patient presents with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, dyspnoea or radiological features on chest CT scan. The diagnosis of ILD/pneumonitis should be made on clinical/radiological findings.

Biomarkers for ILD/pneumonitis are exploratory and they should not be used for diagnosis or monitoring of drug induced ILD/pneumonitis. When evaluating ILD/pneumonitis (regardless of stage) it is highly recommended to include a pulmonary consult, a high resolution CT, PFTs, pulse oximetry and ABGs. It is recommended to delay SYD985 infusions until symptom improvement or until the diagnosis is clarified. It should be considered to reduce the SYD985 dose for subsequent infusions or to discontinue treatment, at the discretion of the investigator.

9.6.1.3. Dose modifications for cardiotoxicity

Patients who develop clinically significant symptomatic cardiac disease during the study will be discontinued.

LVEF assessments will be performed regularly during the study and declines will be handled as summarized in Figure 1.

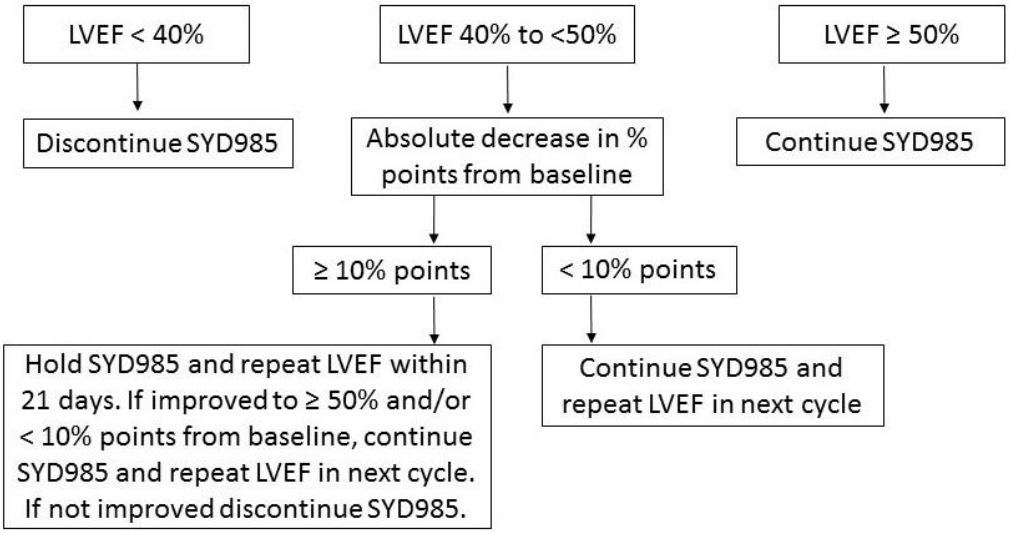

Figure 1: SYD985 dosing in relation to LVEF assessment

SYD985 administration may be delayed to maximally 42 days after the last dose.

9.6.1.4. Dose modifications for haematologic toxicity

For patients who experience a Grade 3 (or higher) haematological event dosing must be delayed for up to 42 days from the last received dose. When the haematologic event resolves to Grade 1 or baseline, patients may continue treatment at the same dose level as before or the dose can be reduced, at the discretion of the investigator.

9.7. Subject emergency card

At start of treatment patients will be handed out a Subject Emergency Card. This card indicates that the patient is participating in a clinical study and contains the patient number and provides details on the study drug that is being studied in the study. The patient is to carry the card at all

times, so that in case of a medical event, the treating medical personnel are aware of the study drug administration. The card also presents an emergency phone number. At the treatment discontinuation visit, the patient is to return the Subject Emergency Card.

10. Concomitant medication

10.1. Acceptable concomitant medication

Patients are allowed to receive supportive care therapies concomitantly during the study (i.e. during treatment and observation phase). Concomitant medication and supportive care should be administered only as medically necessary during the study. Any concomitant medication (including herbal medication and vitamins) must be recorded in full detail (drug, dose, duration of treatment, reason for concomitant medication) in the eCRF. Note that the use of concomitant medication must relate to the documented medical history, an AE or be reported as prophylactic treatment.

After consultation with the medical monitor, palliative radiotherapy may be allowed during the study for e.g. symptomatic treatment of painful bone lesions as long as the lesion is not a RECIST 1.1 defined target lesion and is not administered for tumour control. Study treatment should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of study treatment. Treatment of brain metastases may also be allowed after consultation, unless the (symptoms of) brain metastases are classified as progressive disease for which the patient needs to be discontinued.

Patients will not be routinely treated with an antiemetic regimen prior to SYD985 administration. If a patient experiences grade 3 or greater nausea, diarrhoea and/or vomiting, medical intervention should occur, including prophylactic administration of antiemetic agents for subsequent infusions as indicated. Serious infusion-related events should be managed with supportive therapies as clinically indicated according to standard clinical practice (e.g. supplemental oxygen, β2-adrenergic receptor agonist, and/or corticosteroids). Reduction of the infusion rate and prophylactic treatment should be considered for subsequent infusions, if the patient continues in the study.

Prophylactic lubricating eye drops should be prescribed to patients, to be used 3 times a day or as needed. All patients are advised not to wear contact lenses or rub their eyes during SYD985 treatment.

10.2. Prohibited concomitant medication

Patients are prohibited to receive the following therapies during the study (i.e. during treatment, and observation phase, if applicable):

- All anti-cancer therapies, including:
  - Chemotherapy;
  - HER2-targeting therapy;
  - Other anticancer therapy including immunotherapy or investigational agents;
  - Hormone therapy;
- Radiotherapy (except for palliative care as described in Section 10.1).

Washout criteria apply for anticancer therapy prior to start of study treatment as described in exclusion criterion 1.

10.3. Contraception

Patients of childbearing potential must use highly effective contraception during the study, and up to at least 6 months after last study drug dose. For this study, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as acceptable highly effective birth control methods in line with the recommendations of the Clinical Trial Facilitation Group.[20] Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal);
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable);
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS);
- Bilateral tubal occlusion.

The above contraception is not required in case the patient or sole partner of patient is surgically sterilized, or in case the patient truly abstains from sexual activity (when this is in line with the preferred and usual lifestyle of the patient).

11. Study procedures and assessments

The Study Flow Chart in Section 1.1 summarizes the study procedures to be performed at each visit. Individual study procedures are described below. For details of assessment and reporting of AEs, see Section 12 (Safety Monitoring).

11.1. Obtain informed consent

The investigator or authorized delegate will explain the study to the patient, answer all of his/her questions and obtain the patient's written informed consent before performing any study-related procedure.

The following ICFs will be available in this study:

- Pre-screening HER2 testing-ICF;
- Main-ICF;
- Genetic tumour analysis-ICF;
- Pregnancy-ICF (see Section 12.9).

For potential participants, the pre-screening HER2 testing-ICF should be used to allow the central analysis of HER2 expression on most recently available tumour tissue and to perform a fresh tumour biopsy, if applicable (see also Section 11.8). When the HER2 tumour expression complies with the inclusion criterion and patient enrolment is still open, the patient should sign the Main-ICF before full screening can be started. In addition, the patient will be asked to sign the Genetic tumour analysis-ICF. In case a patient does not consent for this genetic tumour analysis, she can still participate in the study.

The patient can only start study treatment when all inclusion and none of the exclusion criteria are met and enrolment is not yet complete. The patient should start study treatment within 28 days of signing the Main-ICF.

11.2. Demographics and medical history

Demographic and medical history data will be obtained by the investigator or authorized (medically qualified) delegate. The medical history will include at minimum the time of initial and metastatic cancer diagnosis, sites of metastases, prior anticancer therapies (including therapies in the (neo) adjuvant and/or metastatic setting) and details on the hormone receptor (Estrogen and/or Progestrogene receptor) status of the primary tumour and/or metastasis (if available). Only clinically relevant conditions should be reported on the CRF as medical history.

11.3. Inclusion/exclusion criteria

The inclusion and exclusion criteria will be reviewed by medically qualified study personnel to ensure that the patient qualifies for the study. The review of inclusion and exclusion criteria and confirmation of the patient's eligibility will be noted in patient's source documents and appropriate eCRF.

11.4. Physical examination

A complete physical examination will be performed by the investigator or a medically qualified delegate, which should involve abnormalities of at least head/neck, thorax, abdomen, extremities, skin and lymph nodes. Results of the examination should be documented in the patient's medical chart and the eCRF. Abnormal findings at screening are to be reported in the medical history and any clinical significant findings during treatment or at discontinuation as AEs.

11.5. Vital signs, body weight and height

Vital signs assessments include blood pressure, heart rate, body temperature and oxygen saturation by pulse oximetry. Vital signs and weight should be measured at screening and at the time points as indicated in the flowchart (see Section 1.1). Body weight should be used to prepare the IMP infusion bag as described in Section 9.4. Height will be recorded only at the screening visit.

11.6. Eastern cooperative oncology group (ECOG) performance status

The ECOG performance status quantifies the functional status of the patient and should be determined by the investigator or a medically qualified delegate according Table 1.

Table 1: ECOG performance status

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

11.7. Pulmonary Function Testing

Pulmonary function testing should be done according to local hospital standards, and may include spirometry, diffusing capacity of the lungs for carbon monoxide or peripheral oxygen saturation.

11.8. Determination of HER2 tumour status

HER2 tumour status will be determined on most recent available tumour tissue. Tumour tissue taken from previously irradiated areas should not be used for the analysis. Formalin-fixed paraffin-embedded (FFPE) tumour blocks or freshly cut FFPE tissue slides should be sent to a central laboratory for assessment of HER2 expression by IHC and ISH, according to the instructions in the laboratory manual. The remaining part of the tumour block will be returned to the institution. If no archived tumour material is available a biopsy should be performed to obtain tumour material. The biopsy should be performed according to local routine clinical practice.

A patient will be considered eligible if the central laboratory reports a HER2 expression grade 1+, 2+ or 3+ by means of IHC analysis and/or ISH positive.

In general, in case the HER2 tumour assessment was unevaluable, it is allowed to send in new material for re-analysis.

11.9. Genetic tumour analysis

Genetic tumour analysis will be performed by a central laboratory using a clinically validated next generation sequencing test. The analysis will be done on most recent available tumour tissue in combination with blood analysis on germline DNA. Instructions for sample handling and shipment will be provided in the laboratory manual. The patients' tumour mutational profile will be determined, including microsatellite instability and tumour mutational burden. The genetic analysis will cover genes known to be involved in e.g. DNA damage repair pathways, apoptosis, cell cycle and senescence pathways. In addition, gene expression levels by RNA-sequencing may be analyzed as well.

11.10. Haematology and blood chemistry

Blood samples will be taken and analyzed by the local laboratory for haematology and blood chemistry according to local routine clinical practice. In general, the following parameters will be included, but it may differ slightly between local laboratories:

Haematology:	Erythrocyte counts, haematocrit, haemoglobin, mean cell volume (MCV), full and differential white blood cell counts (basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular haemoglobin concentration (MCHC), platelets.
Serum biochemistry:	Albumin, alkaline phosphatase (AP), ALT, AST, total and direct (i.e. conjugated) bilirubin, blood urea nitrogen (BUN) (i.e. urea), calcium, chloride, creatinine, creatine kinase (CK), GGT, glucose, inorganic phosphorus, LDH, magnesium, potassium, sodium, total protein, uric acid.

Sampling should be done as indicated in the flowchart (see Section 1.1). The Day 1 samples should be taken as closely as possible to the start of the new cycle, but may be done up to 3 days before. If the screening assessment is done within 5 days before the first infusion, no new analysis needs to be done at Cycle 1 Day 1. Results of the local laboratory should be available before the start of the new cycle to determine if the patient can continue or not. Patients with screening values not in line with inclusion criterion 7 are not eligible to enter the study (see Section 8.1). For dose modifications or treatment discontinuations based on abnormal laboratory values, see Section 9.6. Clinically relevant laboratory values occurring during the study should be recorded as AEs, preferably as a diagnosis or symptom.

The Sponsor should be provided with a copy of the local laboratory's certification and a tabulation of the normal ranges and units of each parameter collected in the eCRF. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

11.11. Pregnancy test

To exclude pregnancy in women of childbearing potential, a serum pregnancy test should be performed at screening and a serum or urine pregnancy test during treatment.

In the event a patient becomes pregnant during the study, treatment is to be discontinued. The outcome of the pregnancy should be followed up according to the procedures described in Section 12.9.

11.12. LVEF assessment

LVEF should be measured by echocardiogram or MUGA scan according to the routine local clinical practice. Although both echo and MUGA can be used, the method must remain the same per patient from screening onwards. Results of the examinations should be documented in the patient's medical chart and the eCRF.

If LVEF is below 50% the next assessment should be performed during the next cycle as indicated in the dose modification Section 9.6.1.3.

The Day 1 examinations should be performed as closely as possible to the start of the new cycle, but may be done up to 7 days before. Results should be available before the start of the new cycle. Any clinically relevant findings should be reported as an AE.

11.13. ECG assessment

Standard 12-lead ECG should be recorded in supine position after the patients being 5 minutes at rest.
ECGs should be recorded in triplicate for at least 3 seconds with approximately a 3-7 minutes' gap between each of the triplicate readings. ECGs should be obtained before study drug administration for all patients.

Evaluation should be done by the investigator or qualified delegate and any clinically significant abnormalities during treatment should be reported as AEs. Key parameters, including the QT/QTc interval, will be recorded in the CRF. Printouts of the ECGs should be retained for each patient.

11.14. Ophthalmological examination

An ophthalmologist (or qualified delegate) should perform the eye examination, which should at least include a slit lamp exam, corneal sensitivity testing, fluorescence tear film break-up time, and pachymetry. Details of the findings should be recorded in the patient's medical chart and the CRF. Abnormal findings at screening are to be reported in the medical history and any clinically significant findings during treatment or at discontinuation as AEs.

The Day 1 examinations should be performed as closely as possible to the start of the new cycle, but may be done up to 7 days before. Results should be available before the start of the new cycle.

11.15. Tumour evaluation

Measurable and non-measurable lesions must be documented at screening (within 28 days of start study treatment) and must be re-assessed at each subsequent tumour evaluation. Tumour response will be assessed locally according to RECIST version 1.1 until disease progression (for details see Appendix 1).

Scans will be collected and stored by a central imaging laboratory. Independent and blinded assessment of these scans may be initiated at a later point in time when deemed necessary.

Patients must have at least one measurable cancer lesion that is evaluable per RECIST v1.1 (see Appendix 1) to be eligible for the study.

The assessment technique used at screening should be used throughout the study. Technical imaging parameters are defined in the imaging manual. All images are to be submitted to the

central imaging centre. Preferably the same investigator/radiologist should assess all tumour responses for each patient.

CT or MRI scans that were performed before a patient signed the "Main"-ICF may be used to provide screening tumour status as long as they were performed within 28 days prior to start IMP treatment, at the same hospital, with the same technique or machine and preferably by the same individual as those for the tumour assessments during the study. This should be documented in the study files at the site.

Tumour evaluations will be performed every 6 weeks (± 3 days) after the date of start IMP treatment, for the first 24 weeks and every 12 weeks (± 7 days) thereafter. The timing of the tumour assessments is independent of dosing delays. If tumour evaluation falls at the Day 1 of a cycle (in case there are no treatment delays), it can also be performed up to 7 days prior to the Day 1 visit, but should always be done prior to IMP infusion.
If a tumour assessment has to be performed earlier or later, subsequent assessments should be conducted according to the original schedule based on the date of start IMP treatment.

Tumour evaluation at the discontinuation visit is required for patients who discontinue study treatment before first scheduled in-treatment tumour assessment (week 6) and for patients whose previous tumour assessment did not demonstrate PD and was done more than 21 days prior to the treatment discontinuation period. For patients who continue into the Observation Phase as described in Section 11.18.5 there is no need to perform tumour evaluation at the discontinuation visit, they should maintain the same tumour evaluation schedule as during the Treatment Phase.

In cases where there is suspicion of progression before the next scheduled assessment, an unscheduled CT or MRI scan is to be performed, if possible.

11.16. Previous and concomitant medication

Information on all prior received anticancer therapies must be recorded in the eCRF and reviewed in view of the required wash-out period as defined in the exclusion criteria. Other pre-treatment medication and concomitant medication used between 14 days prior to signing the Main-ICF till the treatment discontinuation visit should be recorded in the CRF. The use of concomitant medication must relate to the documented medical history, an AE or be reported as prophylactic treatment. For details on allowed and not-allowed concomitant medication, see Section 10.

11.17. (Serious) adverse events

For details of assessment and reporting of AEs, see Section 12.

11.18. Visit requirements

11.18.1. Screening

Visit requirements are outlined in the study flowchart in Section 1.1. Specific procedure-related details are provided above in Section 11.

Maximally 28 days before start IMP treatment, potential patients will be evaluated to determine eligibility with the in- and exclusion criteria as described in Section 8.1.

11.18.2. Treatment phase

Visit requirements are outlined in the study flowchart in Section 1.1. Specific procedure-related details are provided above in Section 11. Visits are based on a 21-day cycle (± 3 days).

11.18.3. Discontinuation visit

The treatment discontinuation visit should occur at the time study treatment is discontinued for any reason (e.g. due to PD, unacceptable toxicity or withdrawal of consent).

11.18.4. Follow-up

A follow-up visit should be scheduled 30 days after the treatment discontinuation visit. In case a visit is not possible, the patient should be contacted by telephone. During this visit/contact, additional information on (S)AEs that were ongoing at the previous visit will be collected, as well as information on new (S)AEs and concomitant medication used since that visit.

11.18.5. Observation phase

Patients who discontinue study treatment for reasons other than PD (e.g. toxicity), should continue into the Observation Phase of the study and continue tumour imaging according to their original schedule until the time of PD or start of a new anticancer therapy.

11.18.6. Survival follow-up

After the 30-day follow up visit and/or observation period a patient will be followed up for data on disease progression, new anticancer therapies, and survival. These survival follow-up contacts should continue until patient's death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first.

11.19. Study assessments after last patient enrolled

Study assessments will continue as per flowchart (see Section 1.1) until all patients are enrolled and treated in the main study for at least 6 months or have discontinued study participation. Patients who are still on treatment beyond this date may continue treatment, but the frequency and number of study assessments may be reduced as per instructions of the Sponsor. Collected information, such as the toxicity profile of the study drug, will be used to justify the adapted assessment schedule and details will be documented appropriately. Safety assessments and safety reporting will continue in such a way that patient's safety is adequately monitored and documented.

12. Safety monitoring

12.1. Definitions

AE	An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
TEAE	An treatment emergent adverse event is any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.
ADR	An adverse drug reaction is any noxious and unintended response to a medicinal product related to any dose. This definition implies a reasonable possibility of a causal relationship between the AE and the IMP, i.e. the relationship cannot be ruled out.
Unexpected ADR	An adverse reaction, the nature or severity of which is not consistent with the risk information set out in the IB.
SAE	An AE that is/ results in: – Fatal; – Life-threatening; – Persistent or significant disability/incapacity; – Admission to hospital as an in-patient or prolongation of hospital stay; – A congenital anomaly; – Other important medical event. Note when assigning one of the above serious outcomes the following should be referred to: Life-threatening: Any adverse drug experience that places the patient, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that had it occurred in a more severe form, might have caused death. Hospitalization: Admission overnight to an acute care hospital. Procedures done in or visits to a clinic or outpatient facility are not considered serious AEs (SAEs). Admission to a rehabilitation facility, transitional care unit, or nursing home is not considered a hospitalization. Prolonged hospitalization: Any AE that extends a patient's hospital stay beyond the normal expected time. Disability: A substantial disruption of a person's ability to conduct normal life functions. Congenital anomaly: Intrauterine development of an organ or structure that is abnormal in form, structure, or position. Important medical event: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.
SUSAR	A suspected unexpected serious adverse reaction is a serious ADR that is not identified in nature or severity in the risk information set out in the IB or SmPC/PI.
Protocol defined events of special interest (AESI)	The following events are adverse events of special interest and will need to be reported to the CRO expeditiously, irrespective of regulatory seriousness criteria or causality: – Pneumonitis/ILD, – Keratitis grade ≥ 2, – Other ocular toxicity grade ≥ 3 – LVEF decrease to < 50%.

12.2. Adverse event monitoring

Investigators are responsible for monitoring the safety and for providing appropriate medical care in patients who have entered this study (i.e. from the signing of "Main-ICF" onwards). In addition, the investigator remains responsible for following AEs that are serious, drug-related, AESIs, or that caused the participant to discontinue treatment until the event has resolved or until the event has stabilized and determined to be persistent.
Each patient will be carefully questioned and/or examined by the investigator or a medically qualified delegate to obtain information regarding AEs (including SAEs) at each visit until the last protocol specified visit or contact. All AEs will be reported and documented as stated below.

12.3. Adverse events documentation

AEs will be collected from signing of the Main-ICF up to the follow-up visit 30 days after treatment discontinuation. AEs occurring between signing the HER2 testing-ICF and the Main-ICF do not need to be reported, unless it is related to study procedures (i.e. when a tumour biopsy is performed under the HER2 testing-ICF). Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs. Worsening of pre-existing conditions should be reported as a (S)AE.

The investigator/designee is responsible for recording all AEs which have occurred during the study in the patient's medical charts and in the eCRF, regardless of their relationship to the study drug. This includes AEs spontaneously reported by the patient, observed by the investigator/designee or elicited by general non-leading questioning, as well as clinically important deviations of laboratory values from normal ranges. The investigator will review this data and determine the severity and causality as per the definitions provided in Sections 0 and 12.3.2.

Note that by definition AEs include accidents (e.g. motor vehicle accidents) and the reasons for changes in concomitant medication (drug and/or dose), medical, nursing and/or pharmacy consultation, and admission to hospital and surgical operations. Progression of the underlying malignancy itself is not considered to be an AE.

Planned hospital admissions and/or surgical operations/procedures for an illness or disease that existed before the investigational product was given or the patient was enrolled in a clinical study are not to be considered AEs. This needs to be documented clearly in the patient's medical records. Note that any (prolongation of) hospitalization resulting from these planned admissions or procedures are to be recorded as SAEs.

Clinical laboratory data collected during the course of the study, which exceed or drop below the acceptable limits for the patient population and which, based on baseline values, are considered by the investigator to be clinically significant, will be reported as an AE. Note that if clinically significant abnormal laboratory values lead to, or are associated with clinical symptom(s), the diagnosis should be reported as an AE rather than the abnormal laboratory value to allow proper coding.

If a patient's participation is discontinued as a result of an AE, study site personnel must clearly document the circumstances and data leading to the reason for discontinuation.

12.3.1. Adverse events severity

The investigator should determine the severity of AEs according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0) (see the website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). AEs that are not listed in the CTCAE should be graded according to Table .

Table 2: Adverse Event grading (for events not listed in the CTCAE)

Grade	Equivalent to:	Definition
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death	Death related to AE.

12.3.2. Adverse events causality

The investigator will determine the relationship of any AE to the study drug according to the following guidelines:

Unlikely Related: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Probably Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

If a clinical event occurred before the patient received study drug, the causality will be considered as Not Applicable.

12.4. Serious adverse events documentation

The following information must be provided for all SAEs:

- Detailed patient data;

- Exact documentation of the event;
- Exact description of the temporal sequence to the therapy course;
- Documentation of the results of diagnostic and therapeutic measurements;
- Details of the development and outcome including medical judgement;
- As much other supporting data as possible which are important for the judgement concerning the relationship of the SAE to the study drug;
- Critical examination of the relationship to the study drug;
- Name of the reporter.

Events solely due to the progression of underlying malignancy should not be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the underlying disease. In case of progression of disease, the patient must be discontinued from the study.

All SAEs must be followed until resolved or stabilized. The investigator must obtain and maintain files of all pertinent medical data relating to the event. This includes medical records, information and medical judgments from any party who assists in the treatment and follow-up of the patient.

12.5. Reporting of serious adverse events

The occurrence of any SAE from signing of the Main-ICF up to the follow-up visit 30 days after discontinuation visit (regardless of relationship to IMP) has to be notified immediately (within 24 hours of the investigator or designee becoming aware of the event) to the CRO via the electronic data capture system. This also applies to study procedure-related SAEs that occur between signing the HER2 testing-ICF and Main-ICF. In case the SAE cannot be reported via the system, a completed serious adverse event reporting form should be send by fax to the Pharmacovigilance Department of [redacted].

The investigator or designee must promptly report (within 24 hours of becoming aware of the event) clinically significant follow-up information pertaining to the SAE to the CRO. The investigator is obliged to pursue and provide additional information as requested by Sponsor/CRO medical monitor or its designee. The final outcome of the SAE has to be reported in the electronic data capture system or if not available, by fax.

The CRO will report all suspected unexpected serious adverse reactions (SUSARs) to the appropriate Regulatory Agencies, adhering to timelines for reporting outlined as per the (inter)national and local regulatory requirements and ICH GCP Guideline. For this study the Investigator's Brochure contains the reference safety information and is to be used to assess the expectedness of an AE for SYD985.

Investigators must report all SAEs to their Independent Ethic Committee (IEC)/ Institutional Review Board (IRB) according to local requirements.

12.6. Adverse events of special interest

The following events are protocol defined AEs of Special Interest (AESI) and will need to be reported to the CRO expeditiously, irrespective of regulatory seriousness criteria or causality:

- ILD/Pneumonitis;
- Keratitis grade ≥ 2;
- Other ocular toxicity grade ≥ 3;
- LVEF decrease to < 50%.

AESIs should be reported expeditiously to the CRO from start of study drug up to the follow-up visit 30 days after treatment discontinuation, irrespective of regulatory seriousness criteria or causality. Initial AESIs and follow-up information should be reported to the CRO within 5 days of the investigator becoming aware of it, with the same details as for SAEs.

All AESIs must be followed until resolved or stabilized. The investigator must obtain and maintain files of all pertinent medical data relating to the event. This includes medical records, information and medical judgments from any party who assists in the treatment and follow-up of the patient.

12.7. Reporting of death

Deaths that occur during the protocol-specified AE reporting period (from signing of the "Main-ICF" up to up to the follow-up visit 30 days after treatment discontinuation) that are, according to the investigator, due solely to the progression of underlying malignancy, should not be recorded as an (S)AE. Instead, date and reason of death should be documented on the appropriate eCRF. Concurrent AEs should be reported as ongoing at the time of death.

All other deaths that occur during the protocol-specified AE reporting period should be recorded on an SAE eCRF and should be reported expeditiously. During post-study survival follow-up, deaths due to any cause should be recorded on the appropriate eCRF.

12.8. Reporting of serious breaches

A serious breach is defined as a protocol deviation which is likely to affect to a significant degree:

- The safety, physical or mental integrity of the patient in the study; or
- The scientific value of the study.

The investigator should notify the CRO in case of a suspected serious breach within 24 hours of becoming aware of the breach. Additionally, protocol deviations will be reviewed by the Sponsor / CRO during the study and suspected serious breaches will be identified. The Sponsor will define if the suspected serious breach is considered a serious breach. Depending on the nature of the breach, regulatory agencies, ethics committees and investigators will be notified in line with applicable laws and regulations.

12.9. Reporting of pregnancies

If a patient would become pregnant during the course of the study, the investigator or qualified designee must contact the CRO within 5 working days of the investigator or qualified designee

first becoming aware of, or is being notified / informed about the pregnancy. The notification must include a completed pregnancy reporting form. If a SAE occurs in conjunction with the pregnancy, then the reporting time frame for an SAE (24 hours) must be met. The anticipated date of birth or termination of the pregnancy should be provided at the time of the initial report. The patient must be followed up until birth or termination of the pregnancy and the outcome of the pregnancy should be forwarded to the Sponsor/CRO as soon as it is known.

A patient who becomes pregnant during the study must be discontinued from treatment.

13. Criteria for patient discontinuation, replacement and study termination

13.1. Patient discontinuation

Patients participating in this study have the right to withdraw from the study at any time for any reason. A patient must be discontinued from the study when the patient withdraws informed consent. From that moment onwards no new data can be collected from that patient. However, in the case that the patient decides to prematurely discontinue study treatment (e.g. "refuses treatment") or discontinues study treatment prior to progressive disease, e.g. for toxicity or investigators decision, she will remain in the study and will continue all protocol-required follow-up visits according to the flow-chart (Section 1.1). The primary reason for study treatment discontinuation must be recorded in the eCRF and in the patient's medical chart.

The investigator has the right and duty to stop treatment in any case in which emerging effects are of such nature that the benefit-risk ratio is unacceptable to the individual patient. In addition, the investigator is to stop treatment of any patient with unmanageable factors that may interfere significantly with the study procedure and/or interpretation of the results. As an excessive rate of withdrawals can render the study not interpretable, unnecessary withdrawal of patients should be avoided.

The investigator should discontinue a patient from study treatment for reasons including but not limited to the following:

- Disease progression;
- Unacceptable toxicity, including;
    - Clinically significant symptomatic cardiac disease (see Section 9.6.1.3);
    - Clinically significant drug-related toxicity requiring dose delay or interruption which did not resolve within 42 days from the last dose received;
    - Grade 4 infusion-related reaction or a Grade 3 infusion-related reaction which is not responsive to symptomatic medication and/or interruption of infusion;
    - Grade 3 (or higher) ocular toxicity;
    - Grade 2, 3 or 4 ILD/pneumonitis;
- Pregnancy;
- Substantial non-compliance with the requirements of the study;
- Investigator decision based on the patient's best interest;
- Termination of the study by the Sponsor.

Patients who discontinue from study treatment for any of the above reasons should return to the clinic for a treatment discontinuation and follow up visit after the last administration of study drug. Subsequently, these patients will continue to be followed according to protocol for disease

progression (if discontinued for other reasons than PD), unresolved AEs, new anticancer therapies, and survival status as detailed in Section 11.17.5 and 11.17.6.

If a patient decides to completely withdraw from the study participation, the reason for withdrawal from the study must be recorded in the eCRF and in the patient's medical chart. Discontinuation is permanent, once a patient is discontinued it is not allowed to enrol the patient again in the study. When a patient discontinues the study, all efforts should be made to complete and report clinical observations prior to withdrawal from study participation as thoroughly as possible.

In cases where patient contact is lost, a patient should be considered lost to follow-up only after multiple efforts have been made to contact the patient.

13.2. Patient replacement

A patient that discontinues from treatment or study will not be replaced.

13.3. Start and end of study

The overall study begins when the first patient has signed the ICF. The overall study ends when the last patient completed the last study visit, discontinued from the study or is lost to follow-up.

The sponsor may decide to stop further recruitment in the study or at (a) particular site(s) due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure related problems, too low recruitment speed, or any other medical, ethical, or business reason. Additionally, the clinical study will be stopped prematurely if the extent (incidence or severity) of emerging effects/clinical endpoints is such that the benefit-risk ratio to the study population as a whole is unacceptable. In such case, all ongoing patients will be requested to return to the clinic for a final follow-up visit, during which all treatment discontinuation assessments should be conducted. Additional safety monitoring assessments may also be performed, should the reason for termination of the study dictate such assessments.

14. Study evaluation, statistical considerations and data analysis

14.1. General considerations for data analysis

The statistical considerations and analysis plan are summarized in this chapter. A detailed statistical analysis plan (SAP) will be prepared following finalization of the protocol and eCRF and will be finalized well in advance of database lock. Any deviations from, or additions to, the original analysis plan described in the protocol will be documented in the SAP and final study report.

All study variables will be analysed using appropriate descriptive statistical methods. The statistical software used for analysis will be SAS® release 9.4 or higher. Continuous data will be summarized by their mean, standard deviation, median, minimum and maximum. Categorical and ordinal data will be summarized in frequency tables by their absolute frequency (N) and relative frequency (%).

As it is anticipated that accrual will be spread thinly across sites and summaries of data by site would be unlikely to be informative, data from all participating sites will be pooled prior to analysis.

All data from all clinical assessments whether explicitly referred to in this statistics section or not, will be presented in data listings.

Since the secondary endpoints are exploratory in nature, no adjustments for multiple comparisons will be conducted.

14.1.1. Missing data

As the duration of treatment for a given patient will depend on efficacy and tolerability, the duration of follow-up will vary between patients. Consequently, there will be no imputation for missing data.
Handling of incomplete data required for analysis will be detailed in the SAP.

14.2. Analysis populations

14.2.1. Full analysis set

The Full Analysis Set (FAS) comprises all patients who received at least 1 full dose or partial dose of SYD985. The FAS will be used for all listings of raw data, demographic and baseline characteristics, and safety analyses. Unless otherwise specified, the FAS will be the default analysis set used for analyses.

14.2.2. Efficacy analysis set

The efficacy analysis set consists of a subset of the FAS patients who has a baseline and at least one post-baseline tumour evaluation assessment. The efficacy set will be used for the efficacy analysis.

14.3. Timing of analysis

14.3.1. Interim analysis

No formal interim analysis is planned for this study.

14.3.2. Main analysis

The primary analysis will be performed when all patients have been enrolled in the main study for at least 6 months or have discontinued study participation (i.e. completed the last study visit due to disease progression or start of a new anticancer therapy, discontinued from the study or lost to follow-up). All data collected after this date will be summarized and added to the final study report, e.g. as an appendix.

14.4. Demographic and baseline characteristics

Assessments made at the screening visit or before infusion at Day 1 of the first treatment cycle (demographic characteristics, medical history, physical examinations, tumour characteristics, previous or concomitant medication, vital signs, etc.) will be summarized as appropriate.

14.5. Study endpoints

14.5.1. Primary endpoint

The primary efficacy endpoint is ORR based on investigator assessed tumour assessment according to RECIST 1.1. ORR is defined as the percentage of patients with a best overall response of complete response (CR) or partial response (PR). The determination of tumour responses is described in Appendix 1. Both non-confirmed tumour responses as well as confirmed tumour responses (by second assessment at least 4 weeks after first assessment) will be used for efficacy evaluation.

14.5.2. Secondary endpoints

The secondary efficacy endpoints are:

- PFS;
- OS;
- Safety.

PFS (Investigator assessed) is defined as the time from the date of first IMP intake to the date of first documented investigator-assessed disease progression according to RECIST 1.1 or death due to any cause (whichever occurs earlier). Handling of missing values will be similar as described for the primary endpoint.

OS is defined as the time from date of first IMP intake to date of death due to any cause. Patients who are alive or who are not known to have died at the time of the analysis will be censored at the last known date they were alive. Patients with no post-baseline information will be censored at the date of start IMP treatment plus 1 day.

14.5.3. Other endpoints

- To describe time to response;
- To describe duration of response;
- To describe the CBR;
- To explore genomic profile/response relationships.

14.6. Efficacy analysis

14.6.1. Primary objective

The primary objective of the study is to evaluate the anticancer activity of SYD985 with respect to ORR on the basis of investigator tumour assessment.

14.6.1.1. Analysis

14.6.1.1.1. Objective response rate

The primary efficacy endpoint is ORR, defined by RECIST 1.1. ORR will be calculated based on the Efficacy Analysis population. The ORR will be based on calculated responses from investigator lesion assessments. Proportion of patients with ORR will be presented along with 95% CIs. Patients with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage.

14.6.2. Secondary objective

The secondary objectives of this study are to evaluate SYD985 with respect to PFS and OS.

14.6.2.1. Analysis

14.6.2.1.1. Investigator assessed PFS

Investigator assessed PFS will be calculated based on the Efficacy Analysis population. The survivor distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% CI will be presented.

14.6.2.1.2. Overall survival

The analysis for OS will be based on the Efficacy Analysis population. The median duration of survival will be estimated using the Kaplan-Meier method.

14.6.3. Other objectives

Exploratory endpoints of this study include time to response, duration of response and clinical benefit rate.

Time to response is the time between the date of first IMP intake until first documented response (CR or PR) according to RECIST 1.1.

Duration of response applies to patients whose best overall response was CR or PR according to RECIST 1.1, the start date is the date of first documented response (CR or PR) and the end date is the date defined as first documented disease progression or death from any cause (whichever occurs first).

The CBR is defined as the proportion of patients with CR, PR, or SD (SD for 24 weeks or longer). CR, PR and SD are defined according to RECIST 1.1. CBR will be summarized using descriptive statistics. These assessments will be analyzed based on the data observed in the FAS population and will be determined by investigator tumour assessment.

If data allow, exploratory analysis or modeling techniques will be used to investigate the relationship between genomic profile and safety/efficacy parameters.

14.7. Safety data analysis

Safety analysis will be based on the FAS population considering the sections below. Complete details of the safety analysis will be provided in the SAP.
Only treatment emergent AEs (TEAEs), AEs reported to start within the in-treatment period, will be considered. The in-treatment period is defined as the period starting from the first dosing of study drug up to the follow-up visit 30 days after the treatment discontinuation visit. Events starting before first dosing will be presented separately.

14.7.1. Extent of exposure

The total cumulative dose, number of doses, dose intensity, and duration of exposure will be listed and summarized using descriptive statistics.

The number of patients who had any dose modification (including dose delay, dose reduction) and reasons for dose modification will be listed and summarized by treatment.

14.7.2. Treatments

Concomitant medication and non-drug therapies will be listed by patient and summarized by ATC (Anatomical therapeutic chemical classification system) term. These summaries will include medications starting on or after the start of study treatment. Any pre-treatment medications or significant non-drug therapies ending prior to the start of study treatment will be listed.

14.7.3. Adverse events

AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class and preferred term. AEs will be graded by the investigator according to the CTCAE (version 5.0)

An overview table of the number (percentage) of patients with any TEAE, deaths, Serious TEAEs, drug-related AEs, TEAEs leading to discontinuation of treatment, and TEAEs by CTCAE grade will be presented.

Separate summaries will be given for all drug-related TEAE, deaths, Serious TEAEs, TEAEs leading to discontinuation of treatment, and TEAEs by CTCAE grade.

Specific protocol defined AESI have been indicated in Section 12.6. These events are grouped in disease categories which can include one or more safety events. Separate summaries will be given for all AESI categories and drug-related AESIs.

14.7.4. Clinical laboratory evaluations

Changes in laboratory data will be summarized by grade using the NCI CTCAE version 5.0. Changes from baseline will be presented in shift tables for the different lab assessments.

14.7.5. ECG analyses

Standard ECGs parameters (e.g. heart rate, PR, QRS, and QT) will be summarized by scheduled visits. The number of patients who discontinue drug due to cardiac function will be summarized.

14.7.6. LVEF

Absolute LVEF measurements, as well as changes from baseline as a function of time, will be summarized by scheduled visits. In addition, the last and lowest available ejection fraction measurements from each patient will be summarized, along with the corresponding change from baseline. Further analysis will be performed if indicated by the data.

The number of patients who have a LVEF decline to below 50% with an absolute decrease from baseline ≥ 10% points, have a LVEF decline to below 40%, or develop Grade 3 left ventricular dysfunction will be summarized.

14.7.7. Opthalmological exams

Results of the eye examinations, which will include a slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry, will be summarized by scheduled visits.

The number of patients who develop Grade 3 (or higher) keratitis or Grade 3 conjunctivitis, or discontinue study drug due to ocular toxicity will be summarized. More detailed analysis may be performed if appropriate.

14.7.8. Other safety measures

ECOG performance status will be summarized by scheduled visits, in addition, changes from baseline will be presented. The results of body weight and vital signs will be summarized by scheduled visits.

14.8. Sample size

The primary efficacy endpoint of this study is ORR based on investigator review of tumour assessment. Approximately 60 patients will be recruited. Inclusion of HER2 1+/2+, ISH negative patients will be limited to a maximum of 50% of the total sample size. This study is of explorative nature; 60 patients should provide for sufficient safety information and for an ORR estimate with acceptable confidence interval for future decision-making.

15. Study administration

15.1. Regulatory and ethics committee considerations

The Sponsor, CRO and the investigator as well as all other involved parties will ensure that the study is conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (Brazil, 2013), ICH Harmonised Tripartite Guideline for Good Clinical Practice E6, and applicable regulatory requirements.

15.1.1. Approval by competent regulatory authority and IEC/IRB

The Sponsor/CRO will obtain regulatory approval from the competent authority and Independent Ethics Committee(s)/Institutional Review Board(s), where locally required, prior to study start. If any of the approved documents is amended, the Sponsor/CRO will submit these documents for review and subsequent approval as required.

Details of the ethics review committee's composition will be made available conform local regulations. An annual safety/progress report will be provided by Sponsor/CRO to the competent regulatory authority.

15.1.2. Informed consent

The investigator and/or his/her designee will inform the patient in addition to the written patient information about all aspects of the patient's study participation. The designee can be a study nurse to explain procedural and non-medical information on the study, but all medical information must be provided by a medical doctor. When a study nurse provides information on the study, both the investigator and the study nurse are required to sign the ICF.
The written patient information, ICF, and any amendments to these documents must be approved by the competent IEC/IRB and competent regulatory authority.

The investigator and/or his/her designee and the patient must sign and personally date the ICF prior to any study-related activities are being performed. If an authorised representative signs the ICF, all efforts should be made to obtain an additional signature, personally dated, from the patient herself.

The ICF will be signed and the patient and/or the authorised representative should be provided with a copy of the signed ICF. The original is filed with the study documents in the Investigator Site File (ISF).

The decision to participate in the study is entirely voluntary by the patient and/or by the authorised representative. The investigator and/or his/her designee must emphasise to the patient and/or the authorised representative that the consent to participate can be withdrawn at any time without penalty or loss of benefits to which the patient is otherwise entitled.

15.1.3. Investigator reporting requirements

The investigator is responsible for accuracy and completeness of all data recorded in patient's medical and/or study charts and eCRFs. All data recorded in the eCRF are derived from source data unless specifically exempted. Source data will be defined prior to study start but consists in general of the information documented in the patient medical and/or study chart or from information documented in original records and/or certified copies. Corrections to data should be made in a way so that the originally recorded data is still legible and traceable. Any changes should be dated, initialled and explained (if necessary) by the investigator or an authorized member of the investigator's study staff making the correction. The investigator will maintain a file of essential documents of the study as defined by the regulatory requirements, ICH GCP and the Sponsor/CRO (ISF).

15.1.4. Amendments to study protocol

Amendments to the study protocol are prepared when needed and according to Standard Operating Procedures of the Sponsor and/or CRO. Except for administrative amendments, all amendments will be reviewed and approved by the competent authority and competent IEC/IRB prior to implementation.

In the event of an emergency, the investigator may institute any medical procedures deemed appropriate without prior approval by the competent authority and competent IEC/IRB. However, all such procedures must be promptly reported to the Sponsor/CRO and the IEC/IRB.

15.1.5. Investigator compensation

Financial compensation of the investigator and/or his/her institution will be regulated in a financial agreement established between the Sponsor/CRO and the investigator and/or his/her institution.

15.1.6. Coordinating Investigator for Clinical Study Report

A Clinical Study Report (CSR) will be prepared by the Sponsor/CRO to describe the results of the study. One (or several) of the investigator(s) will be selected by the Sponsor to review and approve the final CSR in writing (i.e. coordinating investigator(s)). The Sponsor is to select the coordinating investigator(s) from the participating investigators using the following criteria:

- Must be the Principal Investigator at a site actively enrolling patients and participating in the study;
- Must be willing and capable of completing the necessary reviews and providing approval of the CSR in writing.

15.2. Monitoring and quality assurance

15.2.1. Monitoring

In accordance with applicable regulations, ICH GCP Guideline, Sponsor's and/or CRO's procedures, monitors from CRO will perform the monitoring of this study. Investigational sites will be contacted and visited regularly by CRO staff. The investigational sites will be trained on all study procedures during a site initiation visit and investigator meeting (if applicable).

During the study, the sites will be visited by CRO staff to review the progress of the study, review the data collected, conduct source data verification, perform drug accountability, identify issues and address their resolution. The aim of the monitoring of the study is to ensure that the data collected is authentic, accurate and complete, to ensure the safety of the patients participating in this study and that the patient's rights are protected, and to ensure that the study is performed according to the approved protocol, (inter)national and local laws and all applicable regulations and guidelines. Monitoring will also include remote monitoring by the CRO/Sponsor's staff by evaluation of the data entered in the eCRF.

At study end, the investigational sites will be closed at a final visit conducted by CRO staff to ensure availability of all necessary study documentation, return and/or destruction surplus study materials including study drug, and the adequate archiving of all study-related documentation and materials.

During the whole monitoring process, the investigator agrees to allocate his/her time and the time of his/her staff to the monitor to resolve, discuss and address any study issues.

15.2.2. Direct access to source data/documents

The investigator agrees to allow the authorised staff from CRO/Sponsor, the auditor(s), the IRB/IEC and the regulatory authorities direct access to all relevant documents and source data. Source data, recorded in original records or certified copies, will include the patient's medical and/or study charts which are maintained according to standard clinical practice, read-outs and photos, scans and laboratory reports.

15.2.3. Quality assurance

To ensure compliance with study protocol, ICH GCP, and applicable regulatory requirements, the CRO/Sponsor will conduct quality assurance audits. Regulatory agencies may also conduct inspections of investigational sites. Such audits and/or inspections can occur at any time during or after the study. If such inspection or audit occurs, the investigator and the institution agree to allow the auditor or inspector direct access to source data and all relevant documents and to allocate his/her time and the time of his/her staff to the auditor or inspector to discuss findings and any relevant issues.

The Sponsor/CRO will evaluate processes and data that are critical to assure patient protection and reliability of study results throughout the study. Processes and data that will be evaluated with special attention will be the safety assessments, the ICF process and the primary study endpoint.

15.3. Data handling and records retention

15.3.1. Collection of data and data management

All data collected for this study is to be recorded in the patient medical charts according to standard practice at the investigational site and according to additional requirements of the study. The relevant data will be transcribed from the patient's medical chart into the eCRF. All data that is collected in the eCRF, including the eCRF itself, will be anonymous and will not reveal the patient's name. All documents will be identified by the patient number. The eCRFs must be kept up-to-date so that they always reflect the latest observations on the patients enrolled in the study. CRFs should be signed-off by the investigator as soon as possible after the patient discontinued/completed the study. A monitor will review the completed eCRF. All source data should be kept in conformance to applicable national laws and regulations.

For patients who fail screening, data are to be collected from the time the Main-informed consent is signed until it is determined that the patient has failed the screening. Minimal information should be completed on the eCRF such as patient demographics, disease

characteristics, reason for screen failure and (S)AEs. For patients who fail pre-screening, a subset of this data will be documented.

All original laboratory reports should be available for review in each patient's file. It is important that the original reports are available for review by the investigator on the evaluation of abnormalities for clinical significance.

Data management will be performed by the CRO in accordance with the data validation and data management plan.

15.3.2. Records retention

Following closure of the study, the investigator agrees to maintain all site study records in a safe and secure location. The Sponsor/CRO will inform the investigator about the time period for retaining the documents. The minimum retention time will meet the strictest standards available to that site for the study as given by local laws or Sponsor's standard procedures. By default, and if not otherwise clarified, the retention period will be at least 2 years after the last approval of marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

The CRO and Sponsor should be notified if the study records are moved to an offsite archive location.

15.3.3. Information of investigators about study results

After the CSR is completed, the Sponsor/CRO will provide the report of the study to the investigator.

15.4. Publication policy and inventions

15.4.1. Publication

The Sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database (www.clinicaltrials.gov). In addition, upon study completion and finalisation of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results. Individual manuscripts of partial/site specific data will only be approved after the overall manuscript has been accepted for publication. The data resulting from this study will be proprietary information of the Sponsor.

None of the data resulting from this study will be allowed to be presented or published in any form, by the investigator or any other person, without the prior approval of the Sponsor. The investigator agrees to provide to the Sponsor 60 days prior to intended submission for publication or presentation, review copies of abstracts or manuscripts for publication (including, without limitation, slides and texts of oral or other public presentations and texts of any transmission through any electronic media) that report any results of the study. The Sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and

manuscripts and the right to review and comment on the data analysis and presentation. In case of disagreement, efforts will be undertaken to organize a meeting to discuss and resolve any such issues or disagreement, but the ultimate decision remains with the Sponsor.

Authorship of planned manuscripts for submission to biomedical journals shall be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

15.4.2. Confidentiality

A confidentiality agreement will be executed between Sponsor/CRO and an investigational site representative to regulate the confidentiality of all information and data provided to and/or generated by the investigational site.

15.4.3. Ownership and copyright

All information provided by Sponsor/CRO and all data and information generated by the sites as part of the study (other than patient charts) are the sole property of the Sponsor.

All rights, title, and interest in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the clinical site staff during the course of or as a result of the study are the sole property of the Sponsor. If the financial agreement for conduct of the study does include an ownership provision inconsistent with this statement, that agreement's ownership provision shall prevail.

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APPENDIX 1: Tumour evaluation criteria (based on RECIST 1.1)

Method of assessment

Tumour evaluation will include systemic use of clinical, radiological, and/or other methods to be able to determine tumour progression. Radiological assessment of tumour burden should be performed by CT (preferred) or MRI scan and will follow the RECIST 1.1 criteria.[16]

The same assessment technique must be used throughout the study for evaluating a particular lesion and the same investigator/radiologist should assess the tumour responses for each patient.

Review of tumour response

Tumour assessments should include an evaluation of all known and/or suspected sites of disease, whenever possible. Patients should have lesions selected that can be evaluated at every tumour assessment. Patients with non-measurable disease whose non-target lesions are not assessed at a follow-up visit will be considered unevaluable at that visit unless PD is assessed.

Definition of measurable and non-measurable lesions

Measurable lesions

Measurable lesions are defined as lesions that can be accurately measured in at least one dimension (longest diameter is to be recorded) and have a minimum size of 10 mm when measured by CT scan with a CT scan slice thickness no greater than 5 mm, or have a minimum size of 10 mm with calliper measurements by clinical exam. If scans are used with a slice thickness greater than 5 mm, the minimum size of measurable lesions should be twice the slice thickness

Measurable malignant lymph nodes need to have a minimum size of 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm).

Non-measurable lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are regarded as non-measurable. Leptomeningeal disease, ascites, pleural or peripheral effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

Special considerations regarding lesion measurability

Measurements of bone lesions, cystic lesions, and lesions previously treated with local therapy require special considerations:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or

MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:
- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:
- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Baseline documentation of target and non-target lesions

When more than one measurable lesion is present, all lesions up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions. This means that for patients with only one or two involved organs, the maximum number of target lesions is two or four, respectively.

Target lesions should be selected based on their size (lesions with the longest diameter), be representative of all involved organs, and should be usable for reproducible repeated measurements. The largest lesion may not always lend itself to reproducible measurement, in which circumstance the next largest lesion should be selected.

Lymph nodes should be classified using the shortest axis, where a short axe of < 10 mm as assessed by CT scan signifies non-pathological lymph nodes. Lymph nodes with a short axis ≥ 10 mm but < 15 mm are non-measurable, pathological lymph nodes. Only lymph nodes with a short axis ≥ 15 mm as assessed by CT scan can be used as measurable target lesions.

A sum of the diameters for all target lesions (longest diameter for the non-nodal lesions, and the shortest diameter for nodal lesions) will be calculated and reported as the baseline sum diameters.

All other lesions will automatically qualify as non-target lesions and these lesions will be recorded as 'present' at baseline. Measurement of non-target lesions is not required.

Response criteria

To determine tumour response, the sum of the diameters of the target lesions will be recorded. The target lesions will be evaluated as follows:

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

Partial Response (PR):	At least 30% decrease in the sum of diameters of target lesions, when compared to baseline.
Progressive Disease (PD):	At least 20% increase in the sum of diameters of target lesions, compared to the smallest sum of diameters found in the study, including the baseline sum. In addition, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, when compared to the smallest sum of diameters while on study.

Target lesions should have their actual measurements recorded at each subsequent evaluation. Lesions which after baseline decrease in size to less than 5 mm will be categorized as too small to measure (TSTM) and a default value of 5 mm will be adjudicated.
Target nodal lesions should also have their actual measurement recorded, even when that measurement is below 10 mm (which would signify a normal lymph node). In the event the nodal lesion decreases to less than 5 mm it will be categorized as too small to measure (TSTM) and assigned a default value of 5 mm. For complete responses, the sum of the diameters of the target lesions may therefore be higher than zero while still qualifying for a complete response, due to the inclusion of lymph nodes. In order to achieve a complete response, the target nodal lesion must achieve a short axis < 10 mm.

In addition, the non-target lesions will be evaluated as follows:

Complete Response (CR):	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis)
Non-CR/Non-PD:	Persistence of one or more non-target lesions.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions and/or the appearance of one or more new lesions.

To achieve an unequivocal progression of non-target lesions, there must be an overall level of substantial worsening in these lesions, such that, even in the presence of SD or PR in the target lesions, the overall tumour burden has increase sufficiently to merit discontinuation of therapy. If a new lesion is equivocal because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The patient's overall response assignment on each assessment will depend on the findings of both target and non-target lesions and will also take into consideration the appearance of new lesions. Per tumour assessment, the evaluation of target and non-target lesions will be combined to give an overall response (see Tables A1 and A2).

Table A1: Evaluation of overall response in patients with measurable (± non-measurable) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease			

Table A2: Evaluation of overall response in patients with non-measurable disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease, NE = unevaluable		

Evaluation of best overall response

The best overall response is the best response recorded from the start IMP treatment until 30 days after the last dose of study treatment.

The best overall response is defined as the best response across all assessments. For example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR. When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met, when SD is other-wise the best response, the patient's best overall response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second assessment and does not meet the minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered unevaluable.

To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimal interval of 6 weeks.

APPENDIX 2: Protocol amendment I

CLINICAL TRIAL PROTOCOL AMENDMENT

A single-arm phase II trial to evaluate the safety and efficacy of the antibody-drug conjugate SYD985 in patients with HER2-expressing recurrent, advanced or metastatic endometrial carcinoma who previously progressed on or after first line platinum-based chemotherapy.

Protocol number:	SYD985.003
Development phase:	Phase II
Drug product code:	SYD985
Drug substance:	Trastuzumab vc-seco-DUBA INN = [vic-]trastuzumab duocarmazine
EudraCT Number:	2019-002888-10
IND Number:	146672
Amendment:	Protocol Amendment I (leading to Protocol Version 2.0)
Amendment date:	27 February 2020
Authors:	Synthon Biopharmaceuticals BV: [redacted]

Justification for the amendment

This substantial amendment has been prepared on request of the regulatory authorities and due to additional quality review. The following changes have been included:

- The study flowchart has been updated to include a physical examination at the start of every cycle;
- The study flowchart has been updated to include pulmonary function testing at the baseline visit and whenever clinically indicated;
- In/exclusion criteria in section 8.1 have been aligned with in/exclusion criteria in synopsis;
- Section 9.6.1.1 dose modifications for ocular toxicity have been elaborated
- Section 9.6.1.4 dose modifications for haematologic toxicity have been elaborated

Apart from editorial changes, this has led to the following changes in the protocol text, all included in version 2.0 of the protocol. New text is underlined, deleted text is ~~strikethrough~~.

Synopsis: Study assessments and procedures
Safety assessments will include physical examination, ECOG performance status, vital signs, weight assessment, electrocardiography (ECG), LVEF measurements by echocardiography or MUGA scan, laboratory measurements, ophthalmological examination and adverse event (AE) reporting.

Now reads as:
Safety assessments will include physical examination, ECOG performance status, vital signs, weight assessment, electrocardiography (ECG), LVEF measurements by echocardiography or MUGA scan, laboratory measurements, pulmonary function testing (PFT), ophthalmological examination and adverse event (AE) reporting.

Section 1.1 Study flowchart:
Physical examination has been added at the start of every cycle.
Pulmonary function testing has been added to the baseline visit and when clinically indicated.
The following footnote has been added:

6 Pulmonary Function Testing (PFTs) should be done at baseline and whenever clinically indicated, according to local hospital standard.

Section 8.1.1 Inclusion criteria:
1. Female patients, age ≥18 years at the time of signing first informed consent;

Now reads as:
1. Female patients, age ≥18 years at the time of signing ~~first~~ main informed consent;

Section 8.1.2 Exclusion criteria:

3. History of keratitis;
4. Severe, uncontrolled systemic disease (e.g. clinically significant cardiovascular, pulmonary, or metabolic disease) at screening;
5. 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 leading to permanent discontinuation of treatment;
6. History (within 6 months prior to start IMP treatment) of clinically significant cardiovascular disease such as unstable angina, congestive heart failure (CHF), myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication;
7. Symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, or treatment for brain metastases within 8 weeks prior to start IMP treatment;
8. 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;

Now reads as:

3. History or presence of keratitis;
4. Severe, uncontrolled systemic disease (e.g. clinically significant cardiovascular, pulmonary, or metabolic disease) at screening;
5. 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 leading to permanent discontinuation of treatment;
6. History (within 6 months prior to start IMP treatment) or presence of clinically significant cardiovascular disease such as unstable angina, congestive heart failure (CHF), myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication;
7. Symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, or treatment for brain metastases within 8 weeks prior to start IMP treatment;
8. History or presence 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;

Section 9.6.1.1 Dose modifications for ocular toxicity:

Patients who experience Grade 3 (or higher) keratitis should be discontinued from treatment. For patients who experience other Grade ≥ 3 ocular toxicity, dosing must be delayed for up to 42 days from the last received dose. When the ocular toxicity resolves to Grade 2 or lower patients may continue treatment at the same dose level as before or the dose can be reduced, at the discretion of the investigator. Subsequent dosing delays or treatment discontinuation should be considered in case the ocular toxicity persists. The ocular toxicity should be monitored by an ophthalmologist (or qualified delegate) for recovery.

Now reads as:
Patients who experience Grade 3 (or higher) ~~keratitis~~ ocular toxicity should be discontinued from treatment. For patients who experience ~~other~~ Grade ~~≥ 3~~ 2 ocular toxicity, ~~dosing must be delayed for up to 42 days from the last received dose. When the ocular toxicity resolves to Grade 2 or lower~~ it should be considered to delay dosing for up to 42 days from the last received dose and appropriate treatment with eye drops, cream, or gel should be applied (e.g. steroid containing eye drops). If study drug is interrupted for Grade 2 toxicity it should resolve to Grade 1 or baseline before restarting treatment. Patients may continue treatment at the same dose level as before or the dose can be reduced, at the discretion of the investigator. Subsequent dosing delays or treatment discontinuation should be considered in case the ocular toxicity persists. The ocular toxicity should be monitored by an ophthalmologist (or qualified delegate) for recovery.

Section 9.6.1.4 Dose modifications for haematologic toxicity:
For patients who experience a Grade 3 (or higher) haematological event it should be considered to delay dosing for up to 42 days from the last received dose. Patients may continue treatment at the same dose level as before or the dose can be reduced, at the discretion of the investigator.

Now reads as:
For patients who experience a Grade 3 (or higher) haematological event ~~it should be considered to delay~~ dosing must be delayed for up to 42 days from the last received dose. When the haematologic event resolves to Grade 1 or baseline, patients may continue treatment at the same dose level as before or the dose can be reduced, at the discretion of the investigator.

Section 11.7 Pulmonary function testing has been added:
Pulmonary function testing should be done according to local hospital standards, and may include spirometry, diffusing capacity of the lungs for carbon monoxide or peripheral oxygen saturation.

APPENDIX 3: Protocol amendment II

CLINICAL TRIAL PROTOCOL AMENDMENT

A single-arm phase II trial to evaluate the safety and efficacy of the antibody-drug conjugate SYD985 in patients with HER2-expressing recurrent, advanced or metastatic endometrial carcinoma who previously progressed on or after first line platinum-based chemotherapy.

Protocol number:	SYD985.003
Development phase:	Phase II
Drug product code:	SYD985
Drug substance:	Trastuzumab vc-seco-DUBA INN = [vic-]trastuzumab duocarmazine
EudraCT Number:	2019-002888-10
IND Number:	146672
Amendment:	Protocol Amendment II (leading to Protocol Version 3.0)
Amendment date:	30 September 2020
Authors:	Byondis BV: [redacted]

Justification for the amendment

This substantial amendment has been prepared for the following reasons:

- On April 15, 2020, the name of Synthon Biopharmaceuticals B.V. was changed to Byondis B.V. The legal entity of the company was not changed. The Clinical Study Protocol was updated with the new Sponsor name and logo and converted to a new template.
- Inclusion criterion 3 has been reworded for clarification to assure correct and consistent understanding.
- A time window is added for the pregnancy test at C1D1 to align with the allowed blood sampling window for haematology/chemistry.
- Patient discontinuation criteria updated to reflect the change to Section 9.6.1.1 (Dose modifications for ocular toxicity) as described in Protocol Amendment I.

Apart from editorial changes, this has led to the following changes in the protocol text, all included in version 3.0 of the protocol. New text is underlined, deleted text is ~~strikethrough~~.

Protocol Synopsis and Section 8.1.1: Study population/ Inclusion criteria

3. Eligible patients should have progressed on or after first line platinum-based chemotherapy for advanced/metastatic endometrial cancer. Patients who have had two or more lines of chemotherapy for advanced/metastatic disease are not eligible, taking into account the following:
   - Patients may have received up to one additional line of chemotherapy if given in the neoadjuvant or adjuvant setting. If such treatment was completed less than 6 months prior to the current tumour recurrence or progression it is to be considered first-line treatment;
   - No more than one line of non-cytotoxic systemic cancer therapy (such as immunotherapy, trastuzumab or protein kinase inhibitors) is allowed.

   Note: there is no restriction regarding to the lines of prior hormonal therapy.

Now reads as:

3. Eligible patients should have progressed on or after ~~first line~~ one prior systemic platinum-based chemotherapy regimen for ~~advanced/metastatic~~ endometrial cancer. Patients who have had two or more lines of chemotherapy ~~for advanced/metastatic disease~~ are not eligible~~, taking into account the following:~~.

   Note:
   - Patients may have received up to one additional line of chemotherapy if given in the neoadjuvant or adjuvant setting~~. If~~ provided that such treatment was completed ~~less~~ more than 6 months prior to the current tumour recurrence or progression ~~it is to be considered first-line treatment~~;
   - No more than one line of non-cytotoxic systemic cancer therapy (such as immunotherapy, trastuzumab or protein kinase inhibitors) is allowed.

   Note: there is no restriction regarding to the lines of prior hormonal therapy.

Section 1.1 Study flowchart
The following footnote has been updated:

9. Pregnancy tests (serum test at screening and serum or urinary tests during treatment and at treatment discontinuation) will be performed to exclude pregnancy in women with childbearing potential, and may be done up to 3 days before the start of the new cycle;

Now reads as:

9. Pregnancy tests (serum test at screening and serum or urinary tests during treatment and at treatment discontinuation) will be performed to exclude pregnancy in women with childbearing potential, and may be done up to 3 days before the start of the new cycle. If the screening assessment is done within 5 days before the first study drug administration, analysis does not need to be repeated at the day of first administration;

Section 13.1 Patient discontinuation:

The investigator should discontinue a patient from study treatment for reasons including but not limited to the following:

- Disease progression;
- Unacceptable toxicity, including;
  - Clinically significant symptomatic cardiac disease (see Section 9.6.1.3);
  - Clinically significant drug-related toxicity requiring dose delay or interruption which did not resolve within 42 days from the last dose received;
  - Grade 4 infusion-related reaction or a Grade 3 infusion-related reaction which is not responsive to symptomatic medication and/or interruption of infusion;
  - Grade 3 (or higher) keratitis;
  - Grade 2, 3 or 4 ILD/pneumonitis;
- Pregnancy;
- Substantial non-compliance with the requirements of the study;
- Investigator decision based on the patient's best interest;
- Termination of the study by the Sponsor.

Now reads as:

The investigator should discontinue a patient from study treatment for reasons including but not limited to the following:

- Disease progression;
- Unacceptable toxicity, including;
  - Clinically significant symptomatic cardiac disease (see Section 9.6.1.3);
  - Clinically significant drug-related toxicity requiring dose delay or interruption which did not resolve within 42 days from the last dose received;
  - Grade 4 infusion-related reaction or a Grade 3 infusion-related reaction which is not responsive to symptomatic medication and/or interruption of infusion;
  - Grade 3 (or higher) ~~keratitis~~ ocular toxicity;
  - Grade 2, 3 or 4 ILD/pneumonitis;
- Pregnancy;
- Substantial non-compliance with the requirements of the study;
- Investigator decision based on the patient's best interest;
- Termination of the study by the Sponsor.